

# **Contract Research Services**

## Our Portfolio for Pharma & Biotech

**NMI Technologietransfer GmbH** is a provider of services and products for industrial clients in pharma, biotech and medtech, with a wide range of offerings in the fields of

- Pharmaservices
- Microdevices
- Testing Services

**NMI Technologietransfer GmbH** was founded in 2002 in Reutlingen/Germany, as the commercial subsidiary of the NMI Natural and Medical Sciences Institute at the University of Tübingen, a renowned private research foundation with >200 staff and >30 years of scientific leadership combined with a successful business track record.

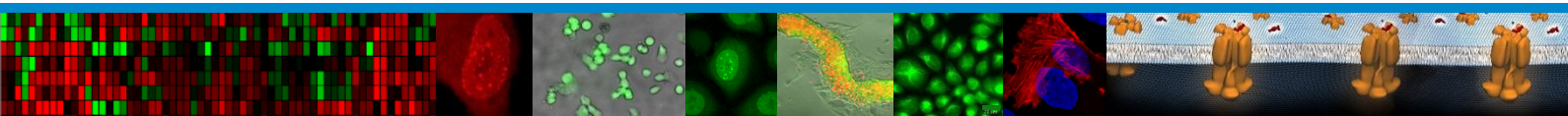
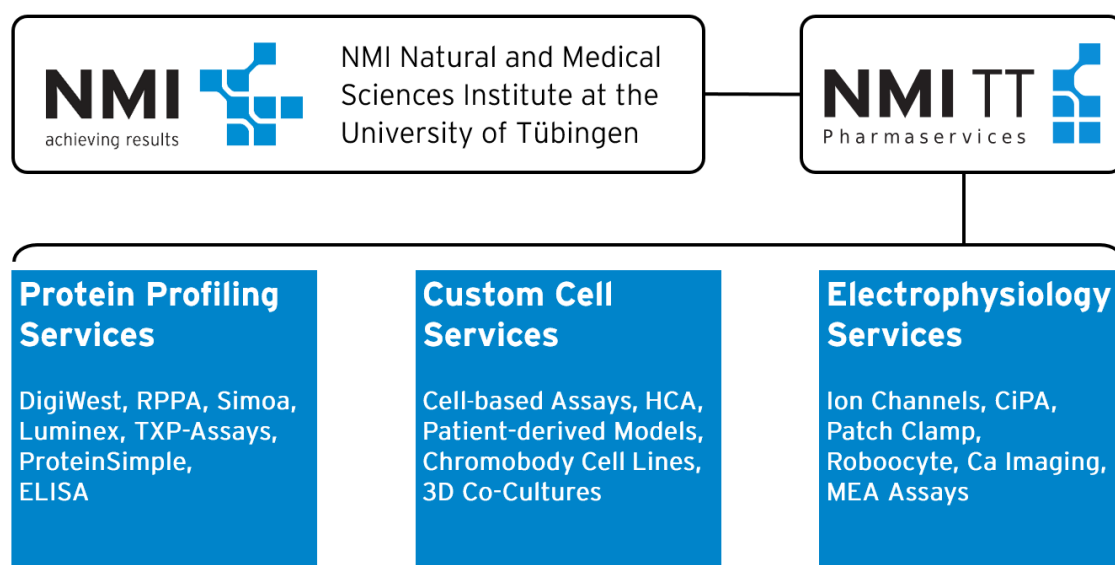
**NMI Technologietransfer GmbH** is committed to providing high-quality research services using cutting-edge technologies.



In our **NMI TT Pharmaservices** division we offer advanced contract research in the areas of

- Protein Profiling Services
- Custom Cell Services
- Electrophysiology Services

All our services are fully customizable to the needs of our clients in the pre-clinical as well as in the clinical space.



Our scientists have built up a long-standing expertise in the area of multiplexed immunoassays.

Applications range from pathway mapping and lead characterisation to biomarker identification and verification, thus covering preclinical and clinical phases alike.

Project scopes vary from assay development and validation studies to routine screening.

Sample types include blood, serum, cultured cells, sections, biopsies and solid tissues.

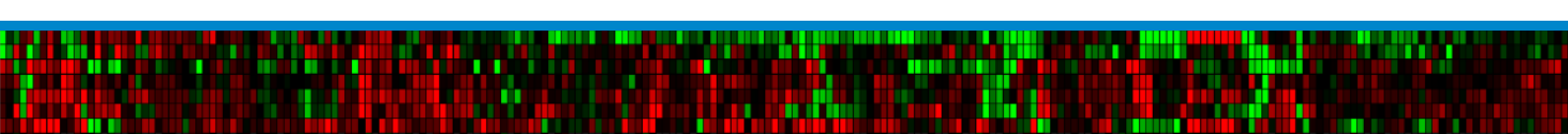
Several technology platforms are available, such that we can offer an unparalleled diversity of technologies to meet the demands of our clients with validated ready-to-go assays as well as highly customised services:

- DigiWest® Multiplex Protein Profiling
- Reverse Phase Protein Arrays (RPPAs)
- Ultra-Sensitive Simoa® Protein Assays
- Standard/Custom Luminex® Assays
- MassSpec-based TXP Immunoassays
- ProteinSimple® Assays
- Standard ELISAs & Western Blots

## Our Protein Profiling Portfolio

	DigiWest	Protein Simple	RPPA	Luminex	ELISA	Simoa	MS-TXP
Sensitivity	10 pg/μg	10 pg/μg	10 pg/μg	10 pg/μL	1 pg/mL	0.01 pg/mL	100 pg/mL
Protein required [μg]	10-60	10-50	30-60	10-100 μL sample	10-100 μL sample	5-100 μL sample	5-50
Analytes per sample	60-800	1-20	20-300	1-60	1-5	1-5	1-25
Samples per study	2-60	dozens	35-hundreds	hundreds	hundreds	hundreds	hundreds
Sample-to-result	5d	3d	5d	4h	4h	3h	1d
Cells/tissues	+	+	+	(+)	(+)	(+)	+
Plasma/serum	-	-	-	+	+	+	+
Urine/CSF	(+)	(+)	(+)	+	+	+	+
Analytes established	1,000+	300+	380+	50+ & vendor kits	vendor kits	25+ & vendor kits	150+
Custom assay development offered	+	+	+	+	+	+	+

PD marker analysis of fresh frozen tumors vs normal liver at defined Ha-ras/B-raf mutation status



## Simoa®: Ultra-Sensitive Protein Profiling

Key features:

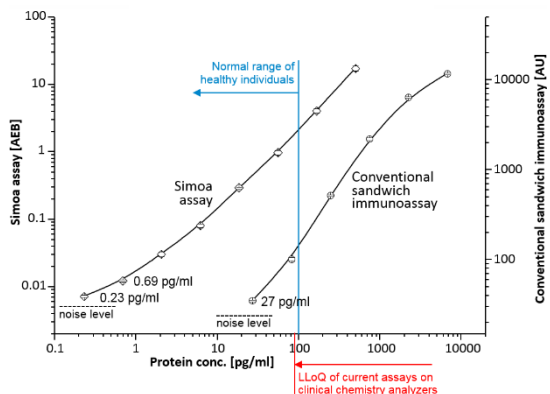
- From 100 up to 1,000-fold higher sensitivity as compared to conventional sandwich ELISAs, using standard or custom Simoa® assays



As an experienced user of Quanterix' technology, we are a leading expert in Simoa® assay services

Applications:

- Biomarker research, quantification of low-abundance analytes for pre-clinical and clinical studies (under GCP conditions)



Case study: Quantification of Procalcitonin, comparing different assay technologies

## TXP Immunoassays for Any Protein in Any Species

Key features:

- Peptide antibody-based enrichment of protein classes for MassSpec quantification allow cross-species protein assays

Applications:

- Translational ADME/Tox assays for cross-species quantification of CYPs, drug transporters, DILI markers, etc.

CYP	TXP Tag
1A1	YIPK
1A2	
2B6	
2C8	FSGR
2C9	
2C18	
2C19	
2E1	SVLK
2D6	
3A4	LPNK
3A5	
3A7	
MDR1	FVEK
CPR	

TXP Antibody



IFFYDSENPPASEVLR



VFFYDSENPPASEVLR



IFFYDSENPPGSEVLR



IFFYDPENPPASEVLR



VFFYDPENPPGSEVLR

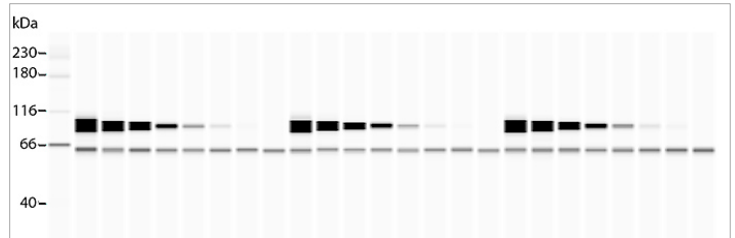
MS-based TXP (Triple X Proteomics) antibody assays for quantification of multiple Cytochrome P450 family members (left); cross-species Paraoxonase assay (right). TXP assays are accessible through our spin-out company Signatope GmbH

## ProteinSimple®: Low Complexity Multiplex Assays

Key features:

- Multiplex profiling of 2-10 analytes in up to 100 samples (cells, tissues, plasma/serum)

Simple Western® assays close the gap between standard ELISA/Western and high-complexity high-throughput immunoassay technologies

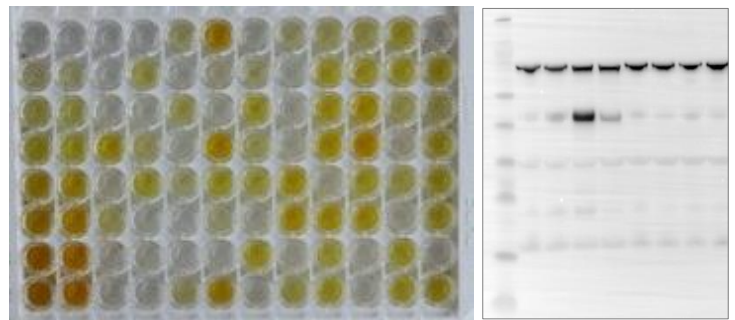


## Standard ELISAs & Westerns

Key features:

- Sensitive quantification of individual or multiple analytes in higher throughput, using commercial ELISA kits, or
- Analysis of single analytes using established or custom antibodies by classical Westerns

We offer standard assays for preclinical research as well as clinical applications

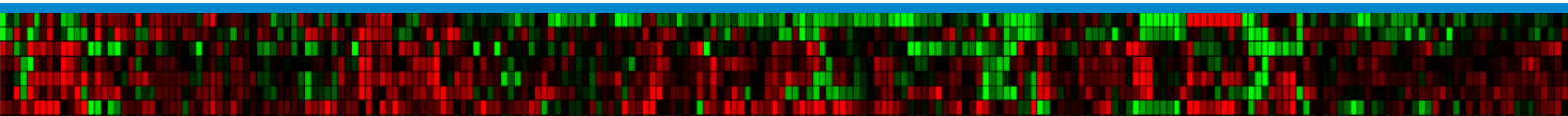
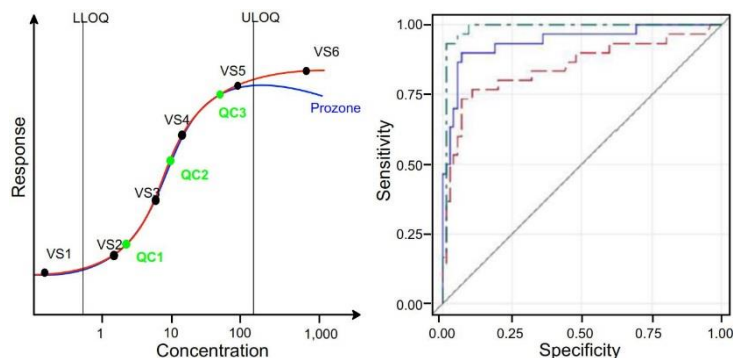


## Standard & Custom Luminex® Immunoassays

Key features:

- Luminex® bead-based assays for plasma proteins (>50 analytes), cell signalling proteins, and serological assays
- Assay development and validation according to CLSI and FDA guidelines

We design, establish and validate miniaturized multiplex assays for PK/PD studies, drug-induced organ injury, pathogen infections, protein-protein interactions etc.

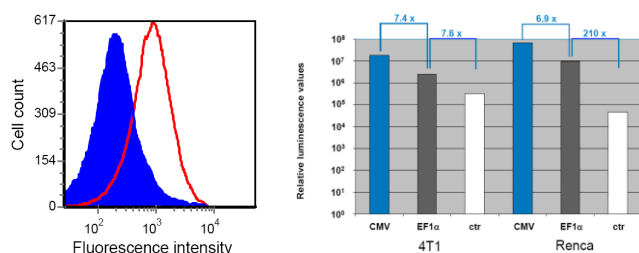




## Target Validation Services

Offerings:

- Cloning of your gene of interest into a suitable expression vector; selection of promoter
- Lentiviral transduction of a cell line / primary cell type of choice
- Selection of stable recombinant cell lines (polyclonal or monoclonal), validated by analysis at the mRNA / protein level
- Characterisation of target protein localisation
- Full range of phenotypic assays

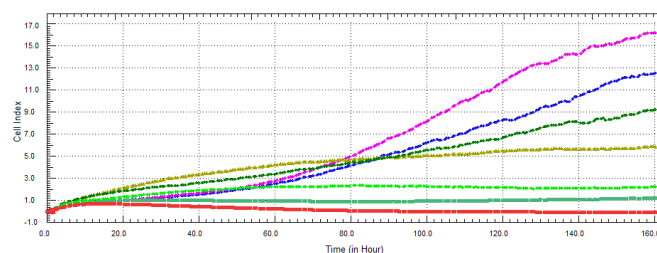


FACS of everexpressed target and promoter titration

## Cell-based Assays

Portfolio:

- Wide range of cell lines & primary models
- Compound treatments, up to small libraries
- shRNA & siRNA assays
- Standard & custom homogenous plate reader assays (proliferation, apoptosis etc.)
- Label-free impedance measurements
- Fixed-endpoint & live high-content assays
- Confocal microscopy, FACS analysis
- Multiplex mRNA & protein profiling



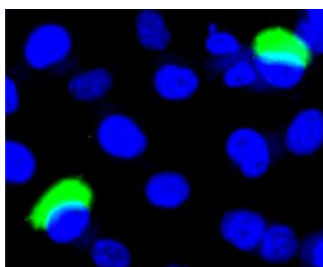
Live microscopy via impedance measurement assays

## CRISPR Genome Editing

Offerings:

- Introduction of specifically site-directed double strand breaks by CRISPR/Cas9
- Target-defective cell lines
- Larger deletions by two double strand breaks
- With an ectopic repair template, specific mutations or extensions can be integrated into the DNA locus

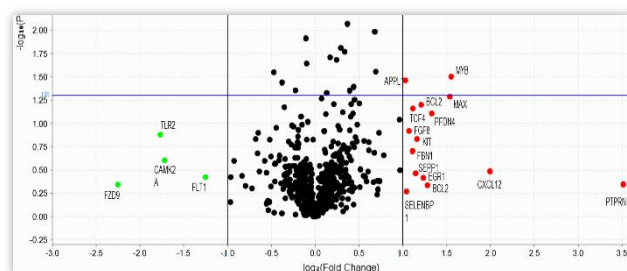
Immunofluorescence image of C-terminal hemagglutinin tagging of endogenous HSP60 in breast carcinoma cells



## mRNA Profiling

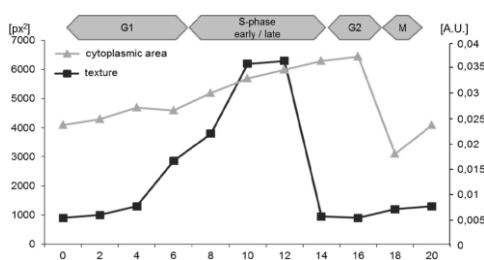
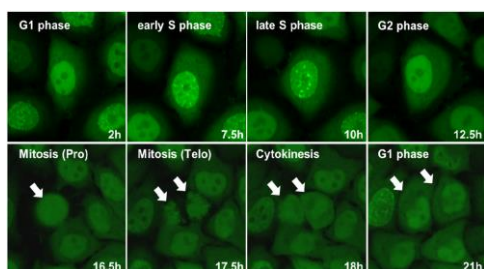
Offerings:

- Single and multiplexed RT-qPCR assays
- OpenArray® Quantstudio™ 12K platform for panels of validated TaqMan® assays
- 600-900 genes of interest
- Pre-designed panels (kinome, inflammation, cancer, stem cells, signal transduction, etc.)
- Fully customisable gene sets available



## High-Content Assays

- Cell-based high-content assays (fixed or live) are fully customizable to our clients' needs
- Small & medium throughput screening studies (using ImageXpress Micro XL screening scope)



Time-lapse microscopy for cell cycle analysis

## Chromobody® Cell Lines

- Chromobodies are intracellular biosensors for high-content analyses in live cells
- Stable Chromobody cell lines are available off-the-shelf; Chromobody expression constructs can be transferred into custom cell lines

- Cell cycle: U2OS, HeLa, PC3, LnCaP, U87MG
- Actin: U2OS, HeLa, MEF, U87MG
- Cell cycle / Actin: HeLa, PC3
- Mito: HeLa, PC3
- Nuclear morphology: U2OS, HeLa
- $\beta$ -catenin: U2OS, HeLa
- DNMT1: HeLa

Exclusive cooperation with  
**chromotek**  
new tools for better research

Currently available stable Chromobody cell lines

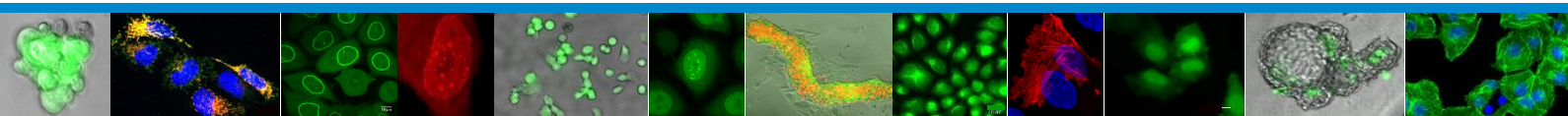
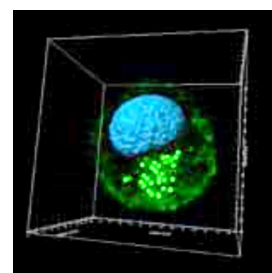
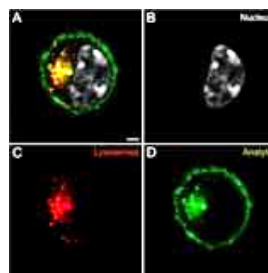
## Internalisation Analyses

Offerings:

- Analysis of monoclonal antibody, ADC and siRNA lead candidate internalisation
- Documentation of cell surface binding and time-dependent internalisation
- Determination of internalisation routes via subcellular segmentations
- High resolution confocal 2D-/3D recordings and time series on fixed & living samples
- 3D & 4D reconstructions and animations
- High-end tools for image acquisition, processing, analysis and data visualisation

Equipment:

- High-end confocal imaging systems (point scanning, spinning disc, structured illumination); software tools for acquisition, processing, analysis & visualisation





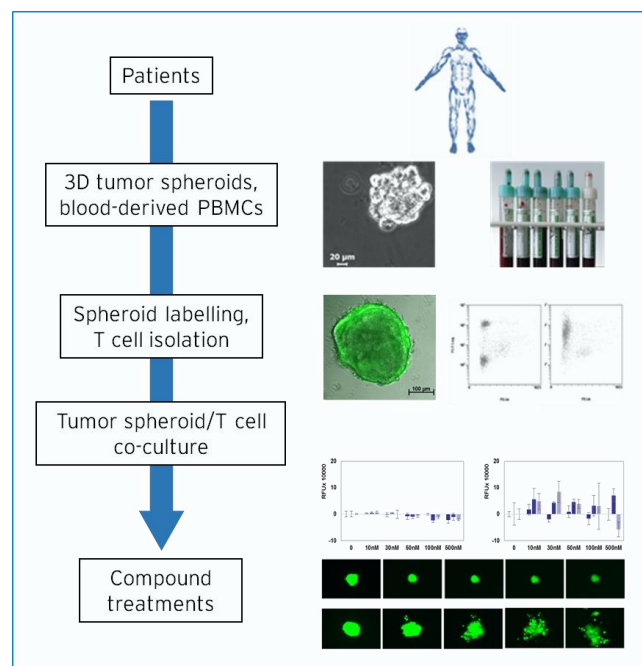
## Immuno-Oncology Services in Patient-Derived 3D Co-Cultures

Key features:

- Panel of primary patient-derived microtumors and PBMCs from the same patient
- Co-culture of microtumors with immune cells (e.g. PBMCs, antigen-specific T cells) and/or compounds
- Performance of homogenous and high-content assays
- Full FTO for commercial studies

Applications:

- Immuno-oncology (IO) drug development
- Quantification of cytotoxicity induced by immune cells (e.g. antigen-specific T cells) alone and in combination with investigational compounds
- Live-cell confocal 3D analysis of tumor spheroid infiltration by T lymphocytes



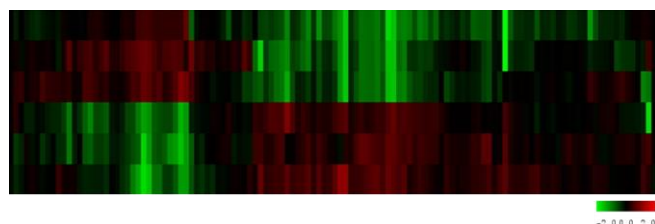
Overview of 3D tumor / T cell co-culture platform

## 3D Tumor Models

- Access to primary patient-derived 3D tumor cell models (PD3D™) through our partner **CELLphenomics**
- Cell-based drug testing and NGS plus protein profiling **CELLPHENOMICS**

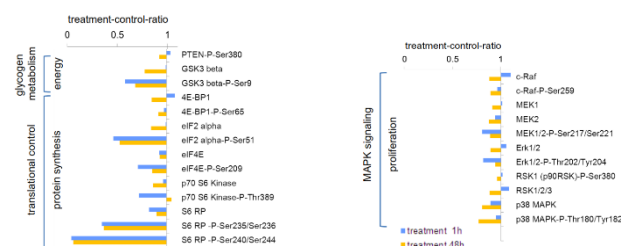


CELLPHENOMICS

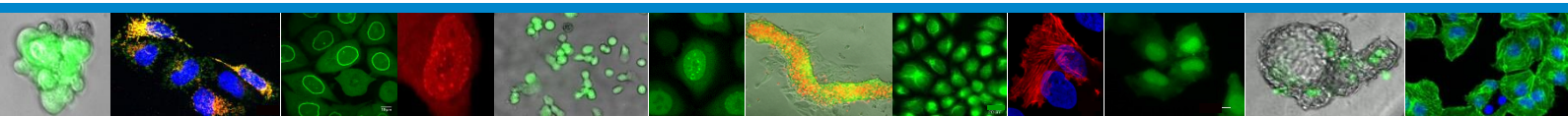


DigiWest profiling of 122 total & phospho proteins in two PD3D tumor models (triplicates)

- Access to cell line-derived homo- and heterotypic tumor microtissues through our partner **InSphero**
- Cell-based drug testing plus mRNA and protein profiling **inSphero**



RPPA profiling of 100 total & phospho proteins in tumor microtissues (Drug vs DMSO, selected data)

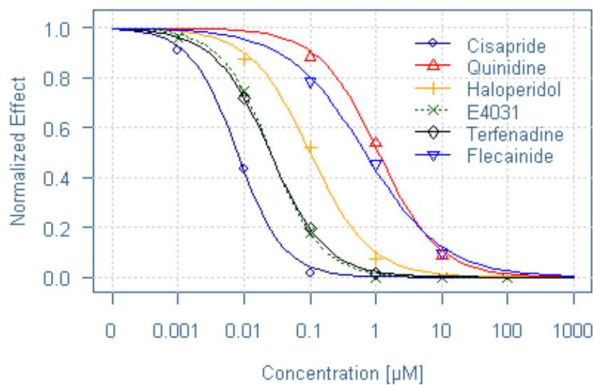


## Automated Patch Clamp

Meeting the higher throughput demands of ion channel screening and early hERG risk assessment, automated patch clamp is an important part of our services. Based on Sophion's QPatch™ technology, combined with our long-standing expertise, we offer high quality ion channel screening together with careful data analysis & thorough data interpretation.

Applications:

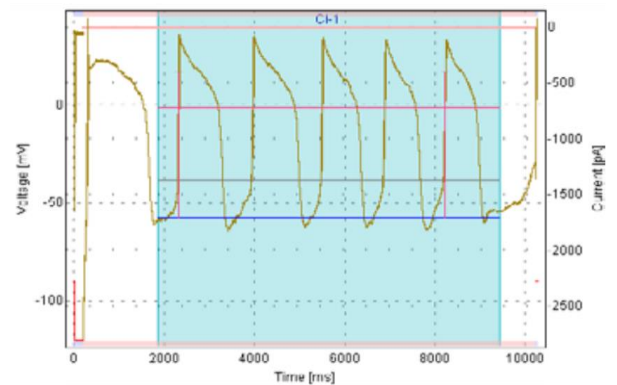
- hERG screening service, to detect hERG safety issues in early drug development
- Screening on other voltage-gated and ligand-gated targets
- QPatch™ outsourcing services



QPatch™ hERG dose-response data (c=4, n=3)



QPatch™, for HT automated patch clamp services



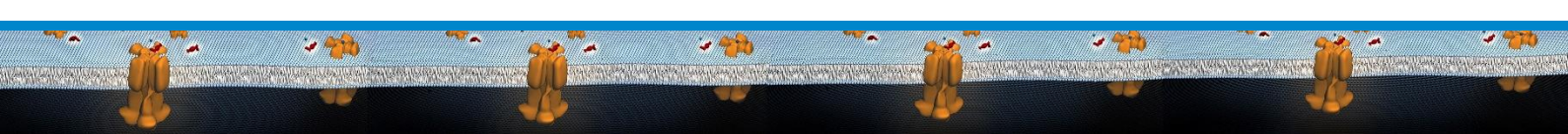
QPatch™ action potentials of stem cell cardiomyocytes

## Patchserver™

- Our proprietary automation solution: Optical selection of the cells to be patch clamped, and fast compound application in the ms range
- Application in drug screening and safety pharmacology

## Manual Patch Clamp

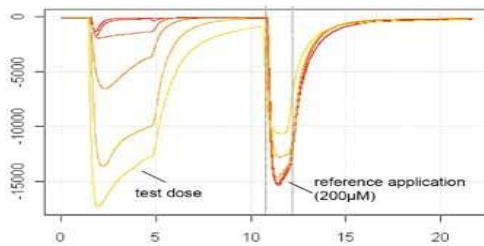
- Gold standard for whole cell patch clamp
- Compound profiling in cell lines, primary & stem cell-derived cell models, tissue slices
- Long-standing expertise in a multitude of indications: heart, CNS, diabetes, pain



## Automated Oocyte Recording

High quality voltage clamp electrophysiology on the Roboocyte™ platform, for drug screening and compound profiling on ion channel targets.

- Flexible assays with short development time for drug screening and compound profiling
- A broad range of ion channels: hERG, SCN5A, P2X, GABA-A, many potassium channels, and customer specific solutions
- Three fully automated Roboocyte™ units with liquid handling robots

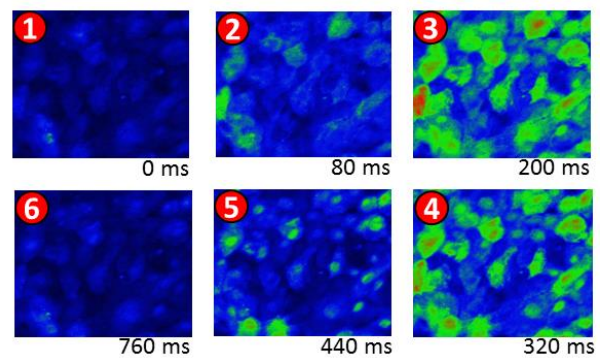


Kinetics of stimulated  $\alpha 4 \beta 2$  AChR in Xenopus oocytes

## Live $\text{Ca}^{2+}$ Imaging

Live cell imaging to analyze drug effects on intracellular ion homeostasis, to test for inotropic effects and proarrhythmic events.

- Zeiss Cell Explorer with attached Yokogawa spinning disk for rapid confocal imaging
- Hamamatsu FDSS for parallel recordings in 96- or 384-well format



Confocal  $\text{Ca}^{2+}$  imaging of beating cardiomyocytes

## CiPA Services

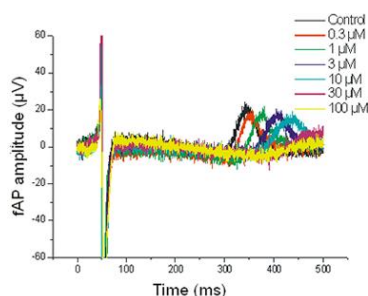
We offer the full range of CiPA (Comprehensive In Vitro Proarrhythmia Assay) services.

Cardiac ion channel services (Qpatch/Patchliner):

- hERG, NaV1.5, CaV1.2 (new cell line), CaV3.2
- KvLQT1/mink, KV4.3, Kir2.1, KV1.5

Cardiomyocyte services (MEA):

- QT interval in vitro measurements

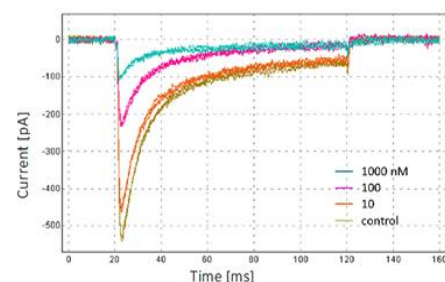


Effect of quinidine on QT interval in vitro

## Our Cav1.2 Cell Line

Key specs of our proprietary Cav1.2 cell line:

- Stable expression of all three subunits of the native Cav1.2 channel ( $\alpha 1c/\beta 2/\alpha 2\delta$ )
- High success rate & reliable performance in automated patch clamp assays
- Run-down free recordings
- Inducible system: easy to maintain in cell culture, adjustable expression level



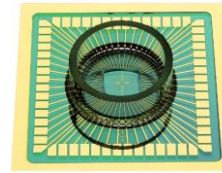
Cav1.2 blocked by nifedipine (Qpatch data)



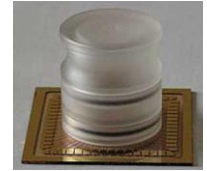
## MEA-based Test Systems

We are offering ex vivo test systems based on Micro-electrode Array (MEA) recordings to analyse complex drug effects on ion channel interactions and cell signaling in:

- Stem cell-derived approaches
- Tissue slices and isolated organs



Acute experiments



Long-term recordings

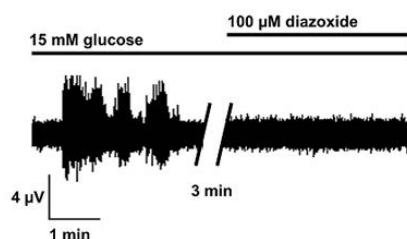
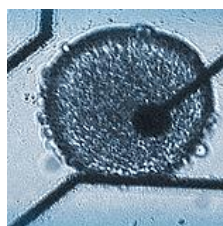
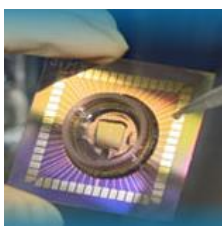
With our more than 20 years expertise in the production of MEAs, we are experts in the development & application of MEA-based drug screening approaches. Current offerings are:

- MEA Beta Cell Screen
- MEA Cardiosensor

## Diabetes Research

Our MEA Beta Cell Screen is an innovative system to test drug effects on beta cell function in a Langerhans islet preparation, and enables:

- Fast & reliable extracellular recording of beta cell oscillatory activity with MEA electrodes
- Determination of drug-induced effects on oscillatory activity of beta cells (alterations in the Fraction of Plateau Phase, FOPP)



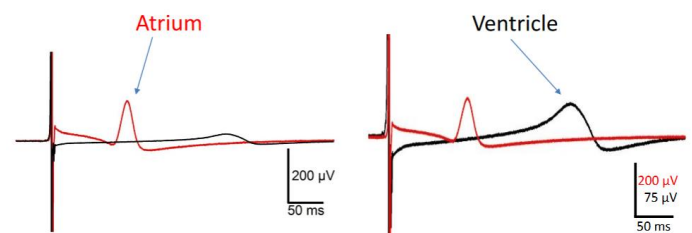
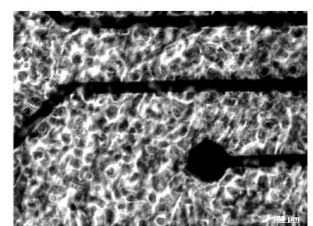
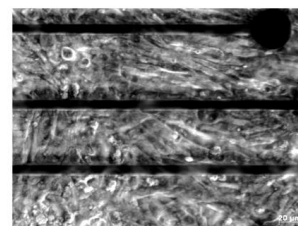
MEA chip with superfusion chamber, Langerhans islet, drug effect on beta cell oscillations

## Safety

Our MEA Cardiosensor is a reliable, robust, relevant & rapid system to test drug effects on cardiac function, including QT interval prolongation & arrhythmia in vitro.

It is based on the extracellular recording of field action potentials (fAPs) of:

- Stem-cell derived cardiomyocytes
- Primary cardiomyocytes from animal models



Atrial vs ventricular cardiomyocytes on MEAs: morphological & electrical differences

**Enquiries:**

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