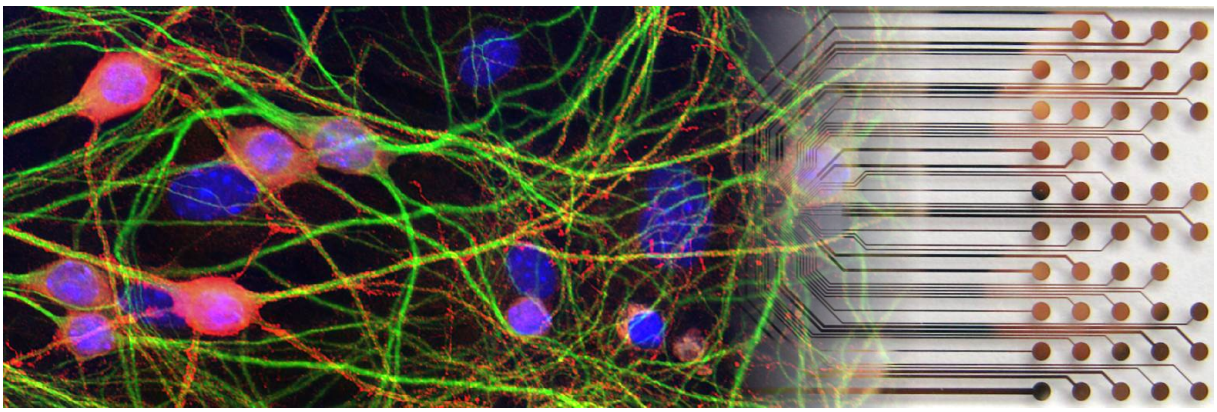
Profiling Pharmaceuticals with Neuronal Network Cultures



Our leading technology with primary neuronal cell cultures on MEA neurochips and sophisticated methods of data analysis is a major step forward in predictive solutions for drug candidate selection, which remains as one of the bottlenecks in neuropharmacology.

NeuroProof® Technology

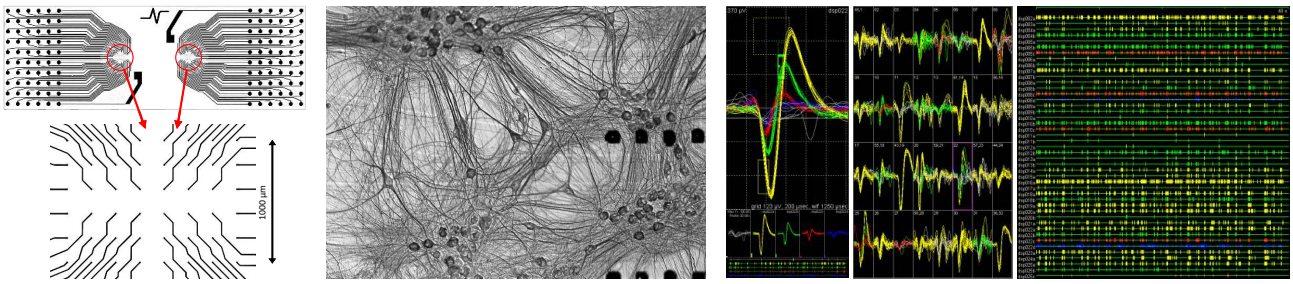
NeuroProof is a high content analysis technology improving the development of new neuropharmaceuticals through its precise assessment of neuronal function.

NeuroProof combines technologies into a powerful and efficient biosensor for preclinical drug research:

- MEA neurochips
- primary neuronal network cultures
- multiparametric data analysis
- pattern recognition methods.

The brain region-specific and substance-specific network activity changes enable the translation from biochemical into a functional responses and the disclosure of unknown modes of action.

The results provide detailed insights with early predictions of beneficial or negative side effects of drugs.



Left: NeuroProof neurochip and electrode area. Center: with primary frontal cortex culture. Right: extracellular recording of network spike train pattern and action potentials.

MEA Neurochips

Recordings of extracellular action potentials from neuronal network cultures on microelectrode array (MEA) neurochips with:

- monitoring of action potential activity patterns of up to 256 individual neurons with 40KHz resolution,
- brain region-specific activity responses,
- substance specific activity changes,
- a high interculture reproducibility and low variability.

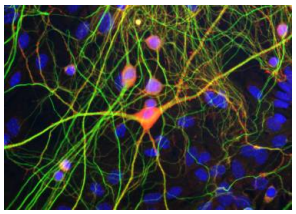
Brain Region Like Neuronal Network Cultures

Neuron/glia co-cultures of dissociated fetal mouse brain

- are composed of non-injured nerve cells which are spontaneously active and stable for more than a year,
- show the full developmental spectrum,
- express *in vivo* host brain region-specific receptor composition with physiologically and pharmacologically relevant responses.

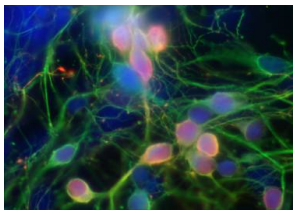
Immunocytochemical Characterization

Receptor Types



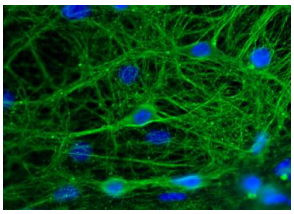
$GABA_A$ receptor (red), neurons (green), nuclei (blue).

Neurotransmitters



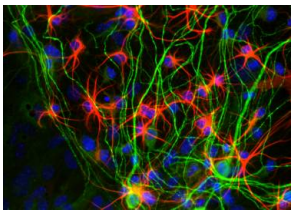
GABAergic cells (red), neurons (green), nuclei (blue).

Tissue Types



Frontal cortex, 28 days *in vitro*; neurons (green), nuclei (blue).

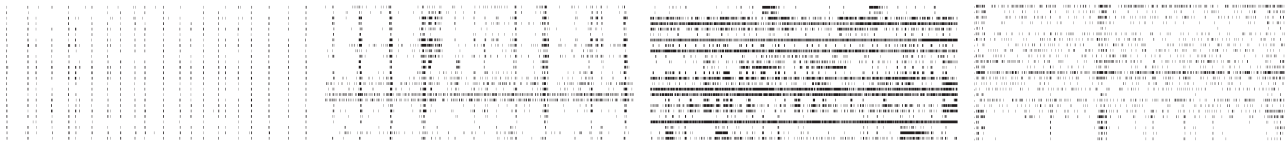
Culture Composition



Astrocytes (GFAP; red), neurons (green), nuclei (blue).

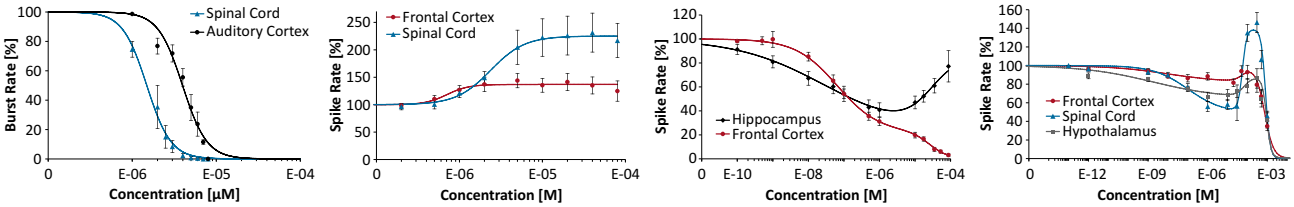
Brain-Region Specific Spontaneous Activity

Frontal Cortex | Hippocampus | Spinal Cord | Hypothalamus

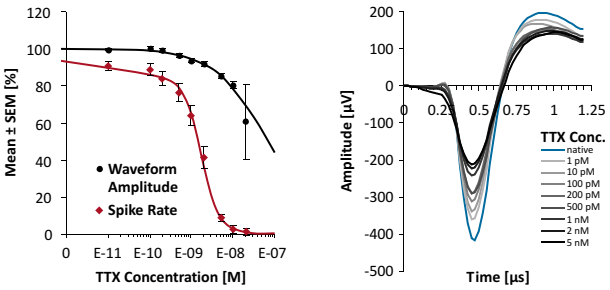


Brain-Region Specific Responses to Various Compounds

Trimethyl Tin Chloride | Bicuculline | Diazepam | Morphine

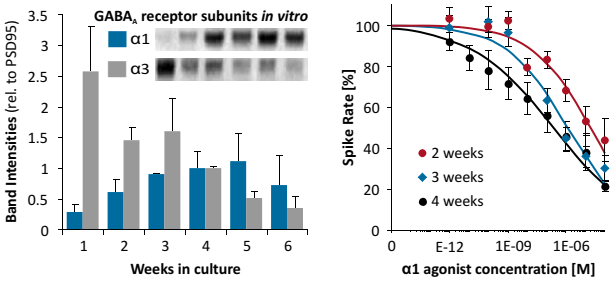


Analyzing Extracellular Action Potentials



Changes in neuronal network activity and in extracellular action potential shape can be recorded and analyzed in parallel.

In vivo Like Receptor Development



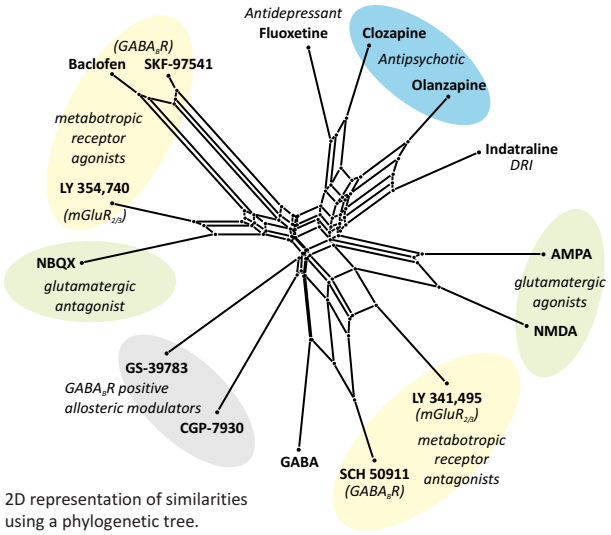
Development of GABA$_A$ receptor composition (left) is reflected in a changing electrophysiological response to Zolpidem (right).

Multiparametric Data Analysis, Pattern Recognition and Substance Database

Every substance induces characteristic network activity pattern changes and thereby its own profile as a functional "fingerprint". This enables drug screening by:

- analysis of complex changes in general activity, burst structure, oscillation, and synchronicity with over 200 spike train parameters,
- and comparison to reference compounds with known response profiles and indications.

The substance profiles in our growing NeuroProof database can be used as a guideline for the development of new pharmaceuticals.



2D representation of similarities using a phylogenetic tree.

Contract Research Organisation Service

Benefit from our high quality standards and long-term experience.

Acute Functional Profiling

- Acute tests, comparison with substance data base
- Receptor blockade experiments
- Isobolographic analyses

Long-term Functional Profiling

- Dose repeated experiments
- Tachyphylaxis
- Developmental studies

Specific Tissue Cultures

- Brain region-specific cultures (frontal cortex, hippocampus, midbrain, hypothalamus, spinal cord)
- Mouse embryonic stem cells
- Induced pluripotent stem cells (iPSC)

Molecular Biology Techniques

- Receptor validation with Western Blotting and immunocytochemistry
- Knock-down models with shRNA
- Overexpression models

Cell Viability Assays

- Diverse biochemical cell viability and cytotoxicity assays (LIVE/DEAD, ATP, LDH and lactate, apoptosis, ELISA, MTT, morphological analyses)

Customized Solutions

- Tailored to your research topic and indication
- Individual cell culture protocols
- Experiments designed specifically for acute or chronic studies
- Investigation and validation of mode of action using semi-quantitative Western Blot and fluorescence microscopy analyses

Application Areas

- Acute, chronic and developmental effects
- Phenotypic screening
- Safety pharmacology
- Drug interactions
- Drug profiling
- Synergistic effects

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