



Drug Discovery and Safety
with **Human iPSC-Neuron**
and **Artificial Intelligence**

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Gene/Cell
Expression vector
transduced cell
line, gene analysis

Protein
Expression of
recombinant protein
Protein identification
Enzyme assay

Drug screening
System validation
Biochemical assay
Cell-based assay

Cell culture
Toxicology
Skin-Lightening,
Moisturizing, Sebum

Material
compound,
polymer synthesis



Peptide
synthesis,
bio-activity assay

**Analytical
chemistry**

**Animal
models**

■ **Neuroscience and Drug Discovery**
in public private partnership

- Revealing neural function in drug discovery with integrated research of neuroscience and electronics



Neuroscience and Drug Discovery

Assessment system and applications with ;

- **Human iPSC-neuron**
- **MEA** : Microelectrode array for detection of extracellular action potential
- **AI** : Proprietary Artificial intelligence and multivariate analysis for pharmacology

(1) Human Neurons

- **CNS** : Cortical neuron, Dopaminergic neuron ...
 - **Sensory neuron, Motor neuron** ...
 - **Glia cell**: Microglia, astrocyte, ...
- ➔ Difference of cells from rodent to human

(2) Efficacy and Pharmacology

- **Disease-models**: siRNA-KD, gene-mutation for PD, ALS, Alzh, ...
- **Patient-derived iPSC neuron**: HD, Dravet (Organoid), ...

(3) Toxicology

- **2D**: Ion channels/receptors on cortical neuron
- **2D**: Addiction in dopaminergic neuron
- **2D**: Adverse event in sensory neuron
- **3D**: Application of cerebral organoid



Pharmaceuticals
Biotech
Academia
Research Inst. ...

Platform Technology (Selected)

■ **CNS : Seizure, Addiction**

- Principal Component Analysis to Distinguish Seizure Liability of Drugs in Human iPSC-Cell-Derived Neurons (Toxicological Sciences, 184:265, 2021)
- Can we panelize seizure? (Toxicological Sciences, 179:3, 2021)
- Toxicological evaluation of convulsant and anticonvulsant drugs in human induced pluripotent stem cell-derived cortical neuronal networks using an MEA system (Scientific Reports, 8:10416, 2018)
- Evaluation of drug addiction using human iPSC-dopamine neuron (Japanese Society of Toxicology, 2022)

■ **Sensory neuron: Pain assessment**

- In vitro pain assay using human iPSC-derived sensory neurons and microelectrode array (Toxicological Sciences, 188:131, 2022)

■ **Motor neuron: Neuromuscular disease** (In preparation for publication)

- ALS and related diseases models with human iPSC-motor neurons
- Efficacy for mutated neurons by gene-editing of a disease gene
- Inhibition effect for accumulation of mutated proteins in patient motor neurons

■ **Axon tracking : conduction velocity, synaptic plasticity**

Versatile live-cell activity analysis platform for characterization of neuronal dynamics at single-cell and network level (Nature Communications, 11:4854, 2020)

■ **Artificial intelligence** : Raster plots machine learning to predict the seizure liability of drugs and to identify drugs (Scientific Reports, 12:2281, 2022)

■ **Drug response** : Physiological maturation and drug responses of human induced pluripotent stem cell-derived cortical neuronal networks in long-term culture (Scientific Reports, 6:26181, 2016)



HESI



■ Analysis: Artificial Intelligence

Analysis

Record

Culture

【Deep learning】

- Image recognition with raster plot of positive controls
- Weighted pattern recognition extracting feature value
- The AI is created to pile up multi-layers of algorithm.

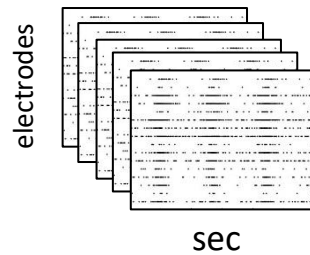
【Identification】

The AI identifies/classifies feature value between control and test compounds to toxicity risk and efficacy.

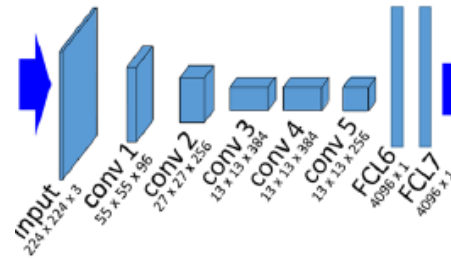
【Advantages】

- A wide range of accurate identification with 4000+ parameters.
- Hi-sensitive evaluation in weak neural firing.

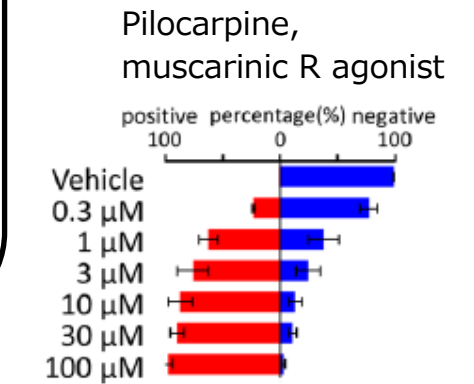
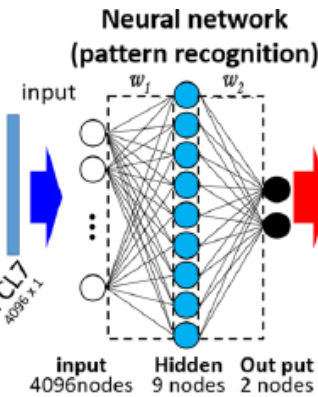
1. Separated spike stamp table



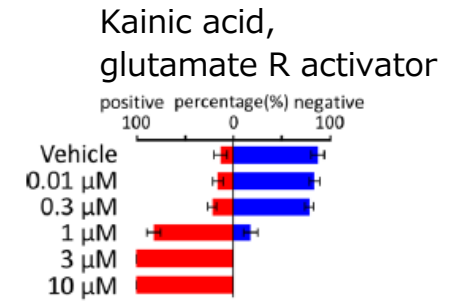
2. Image Recognition (image recognition)

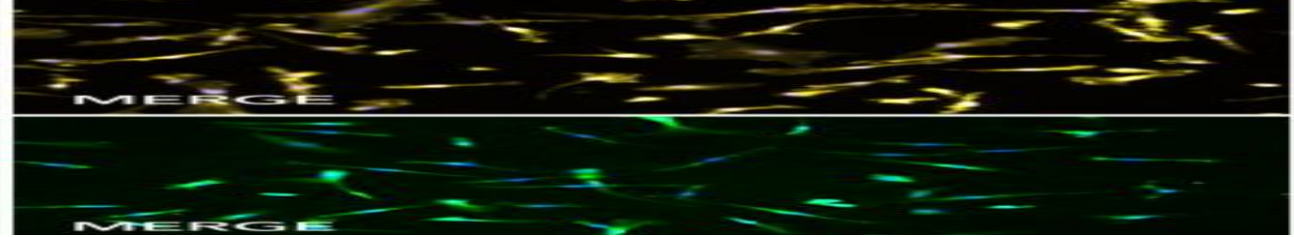
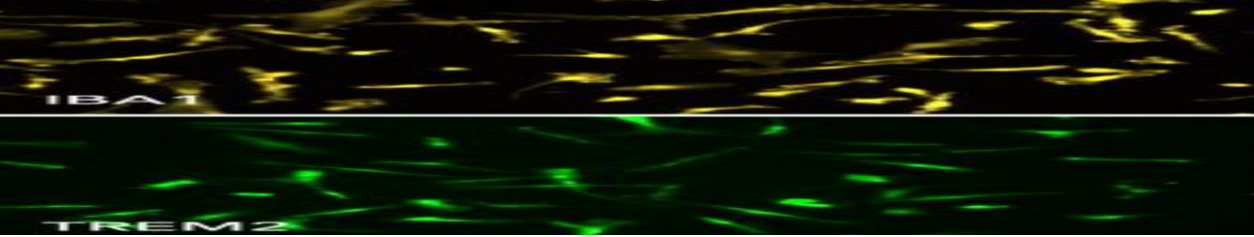


3. Pattern Recognition



4. Identification





Human iPSC-microglia function assays

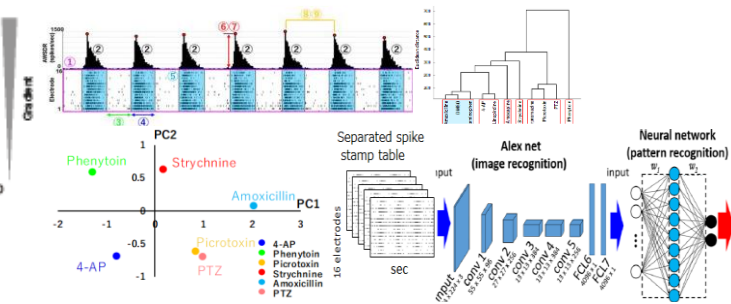
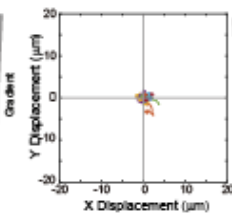
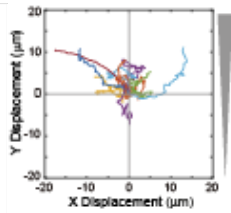
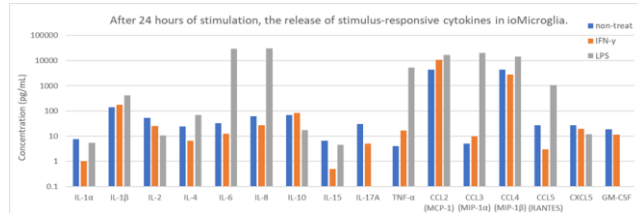
■ **Microglia** is a significant target of drug discovery, activated by neurodegeneration, brain injury and infection, possessing various functions of phagocytosis, inflammatory factor releasing and chemotaxis to lesion.

Microglia culture

- Phagocytosis of particles of Amyloid β -42, bacteria ...
- Inflammatory cytokine release
- Chemotaxis

Co-culture with human iPSC-neuron

- Recording of action potential
- Analysis with AI and multivariate statistics for drug efficacy, pharmacology, toxicology ...





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