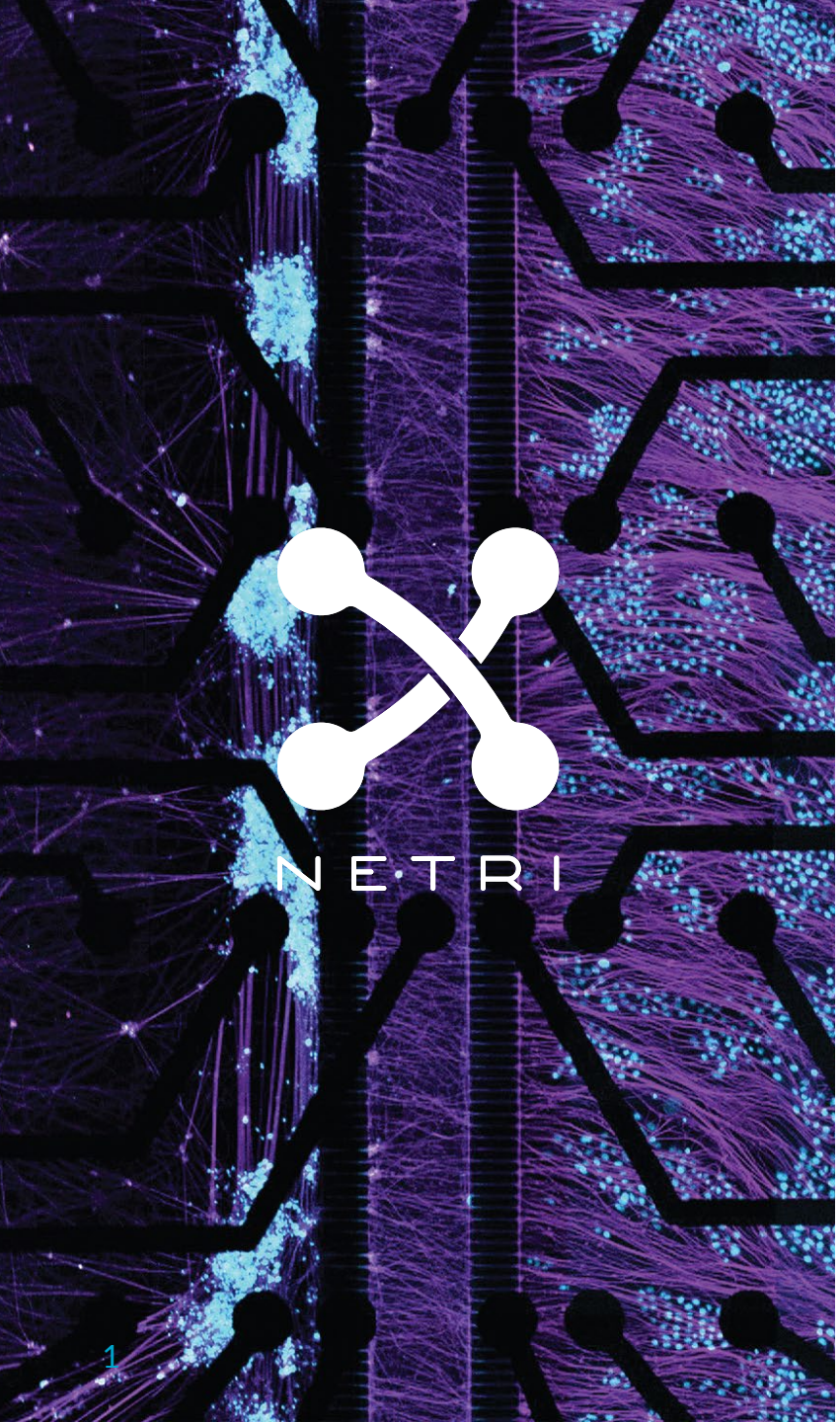


An in vitro skin-on-chip model for studying neuron-keratinocyte interactions in sensory response through electrophysiology.

Thibault Honegger[a], Thomas Bessy[a], Anthony Martinez[b], Camille Baquerre[a], Corinne Grégoire[b], Aurélie Batut[a], Aurore Berthelin[b], Louise Dubuisson[a], Séverine Teluob[b], Audrey Azéma[a], Laurène Roussel Berlier[b], Damien Lelièvre[b] & Alexandre Guichard[a]*

[a] *NETRI, 76 rue Georges Gouy, 69007 Lyon, France*

[b] *EPISKIN, 4 rue Alexander Fleming, 69007 Lyon, France*

MPS World Summit 2026 | Session 3.5

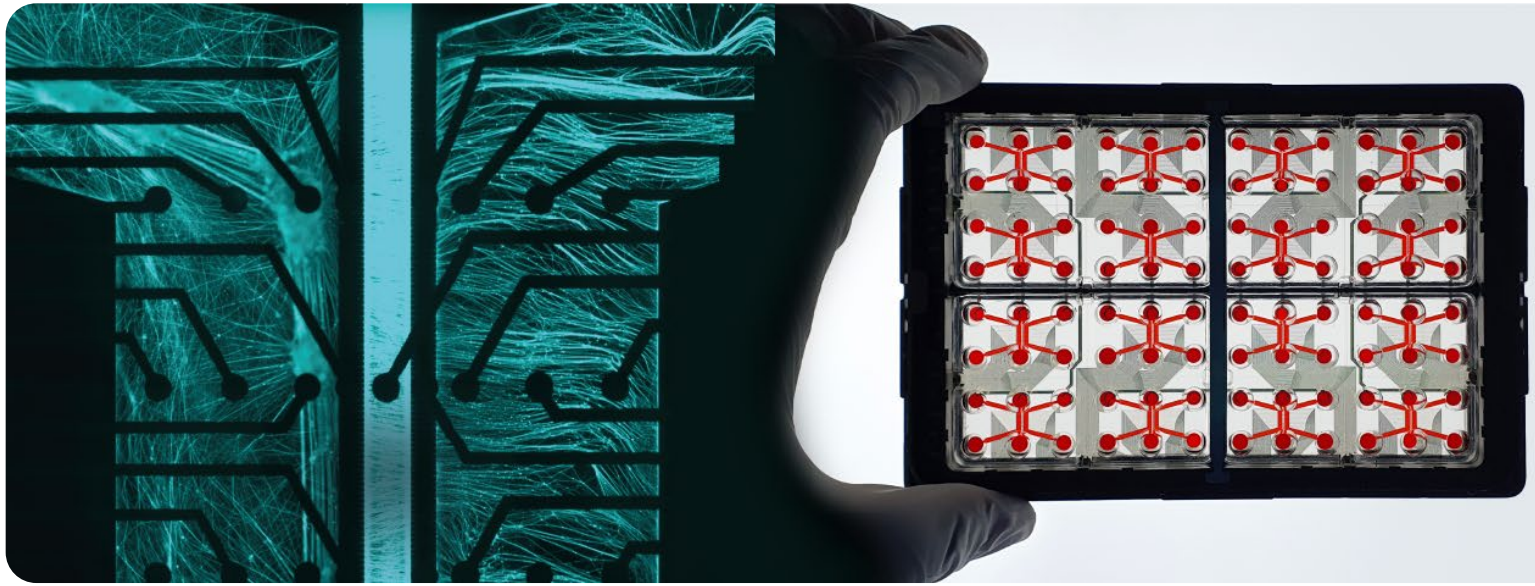
2026 May 28, Washington

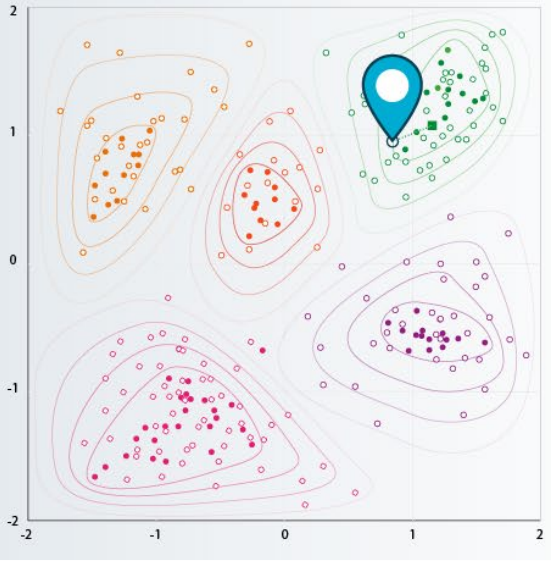
BOOTH #618

L'ORÉAL
RESEARCH & INNOVATION | ADVANCED RESEARCH

WHO WE ARE

FOUNDED IN 2018
32 PEOPLE | MULTIDISCIPLINARY TEAM
16 PATENTS | 100+ CLIENTS



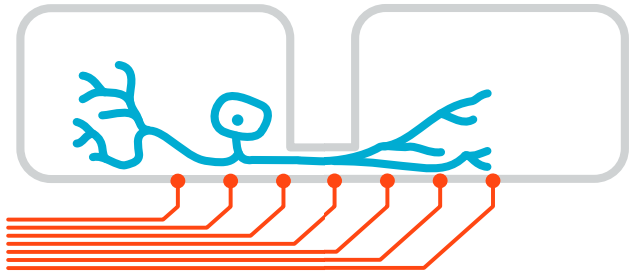


NETRI is an industrial TechBio
dedicated to enhancing human health
through the discriminating power of the nervous system.

ENDLESS POSSIBILITIES

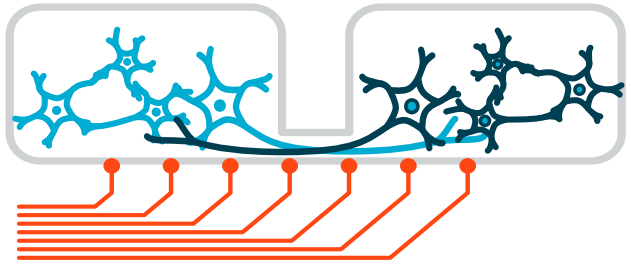
2D ORGAN MODELS

SENSORY



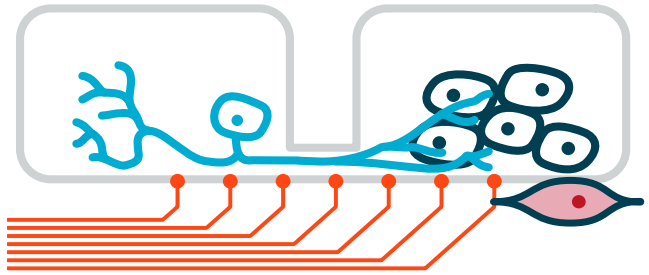
SIMPLE PNS

CNS



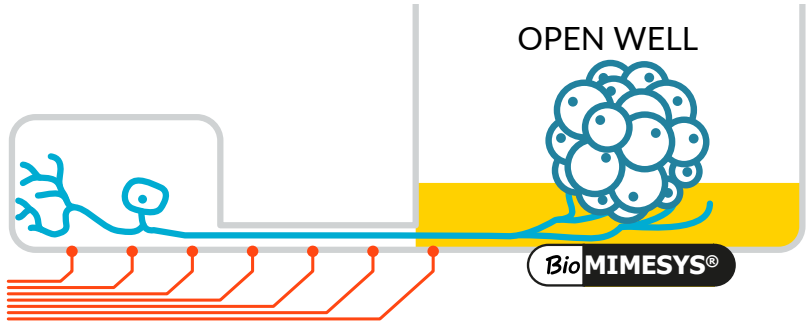
CNS

MTN

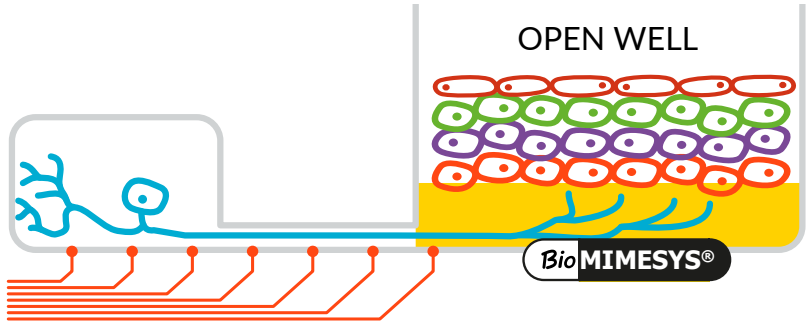


MUSCLE
SKIN
GUT
...

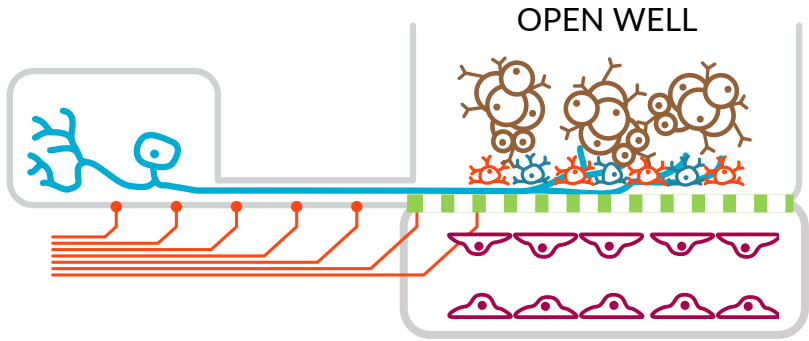
3D ORGAN MODELS



SPHEROIDS
ORGANOIDS



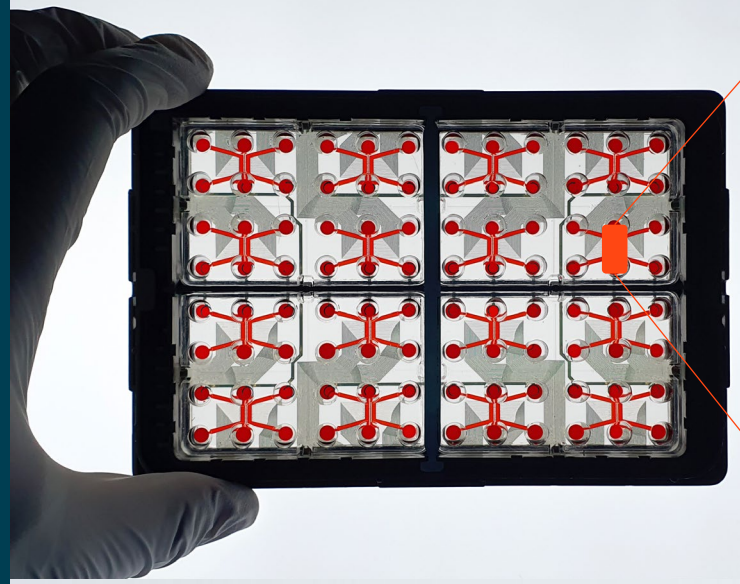
2D/BIOPSY
AIR/LIQUID
INTERFACE

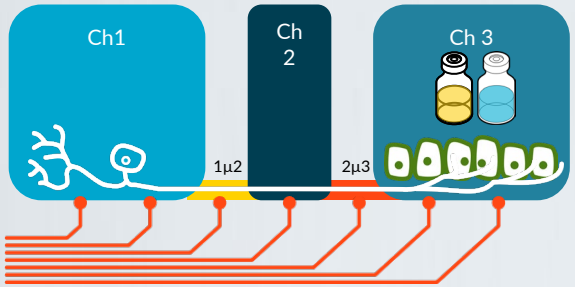


MEMBRANE

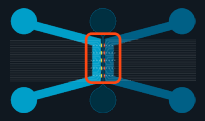
INNERVATION

THE ONLY COMPARTMENTALIZED ELECTROPHYSIOLOGY PLATFORM FOR INNERVATED MODELS

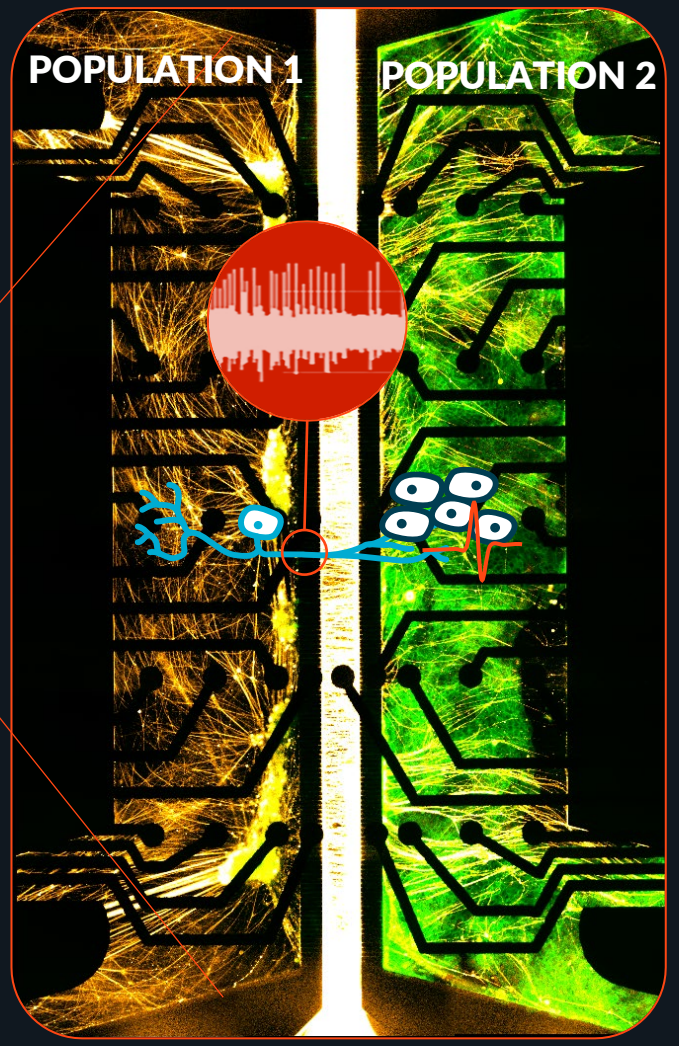




WORLD'S FIRST COMMERCIALY AVAILABLE
COMPARTMENTALIZED ELECTROPHYSIOLOGY PLATFORM



DuaLink™
For 2 co-cultures

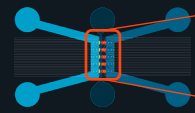


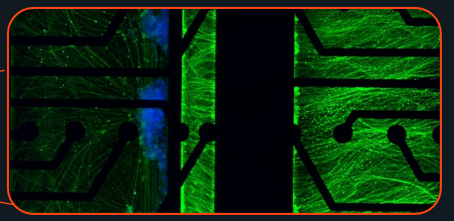
Extracting 500+ Variables
from electrophysiological signal

WO23187279,
WO23187280

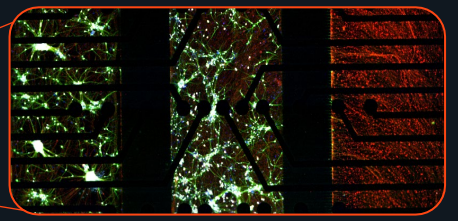
2D ORGAN MODELS

DuaLink™ Shift
For synaptic isolation



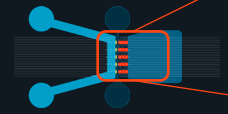


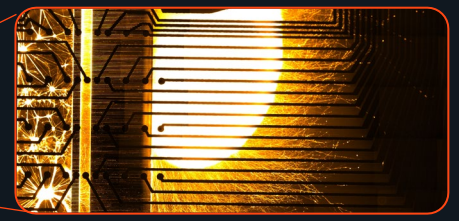
TriaLink™
For 3 co-cultures



3D ORGAN MODELS

DuaLink™ Well
For 3D co-cultures
Innervation



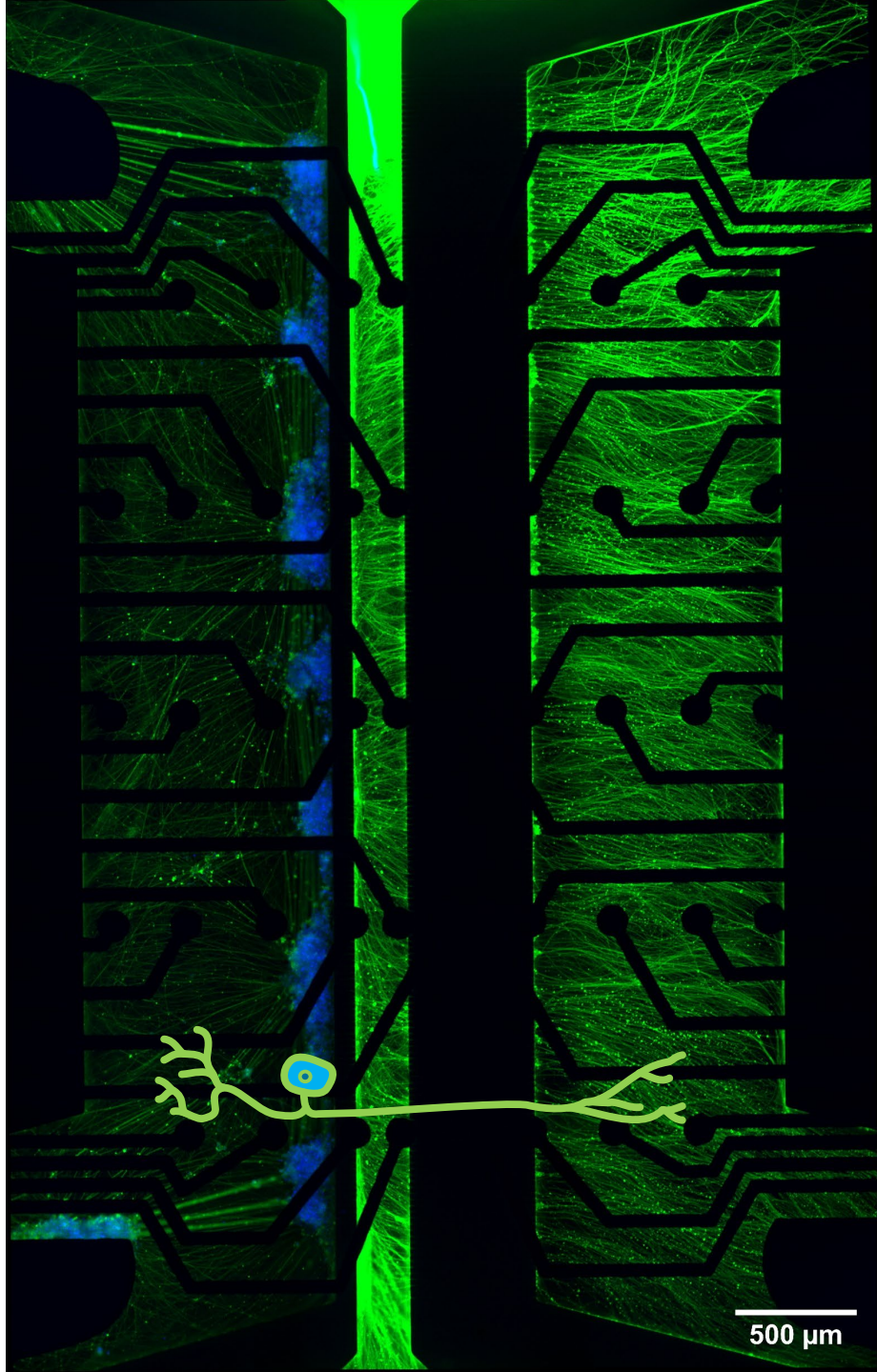


Duplex™ Link MEA
For 3D co-cultures
Innervation &
Vascularization

CONTEXT OF USE

SKIN SENSATION IS A COMPLEX MULTICELLULAR, SPATIALLY ORGANIZED PROCESS

- **Itch, pain and discomfort** responses are mediated by the interaction between sensory neurons and keratinocytes
- **Sensory neurons endings** detect painful, thermal and pruritic stimuli and transmit peripheral signals to the central nervous system through the ganglion and **play a role of biosensor**
- **Keratinocytes in the epidermis** express **sensory receptors** and **release mediators** that modulate neuronal activity.
- Thus, there is an **anatomical compartmentalization** of the different cellular subtypes.
- Dermatology and cosmetic development needs human-relevant models that can report functional sensory responses.



OVERVIEW

EXISTING MODELS MISS EITHER HUMAN RELEVANCE, SPATIAL ORGANIZATION OR FUNCTIONAL READOUT

- Design requirements for a translational innervated skin MPS

CURRENT LIMITATION

- Neuron-free skin models cannot capture sensory signals
- Animal model may not reflect human sensory signaling and are banned in cosmetic
- Co-cultures often lack soma/axon separation and consist of a mix of cells
- Readouts are frequently endpoint, indirect (dosage) or low-throughput

REQUIRED CAPABILITY

- Functional human iPSC-derived sensory neurons
- Human primary keratinocytes
- Direct interaction between neurons and keratinocytes
- Selective stimulation of distal axonal endings and keratinocytes
- Real-time, non-invasive electrophysiological recording

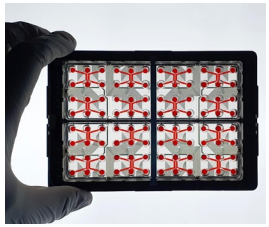
STUDY IMPLEMENTATION

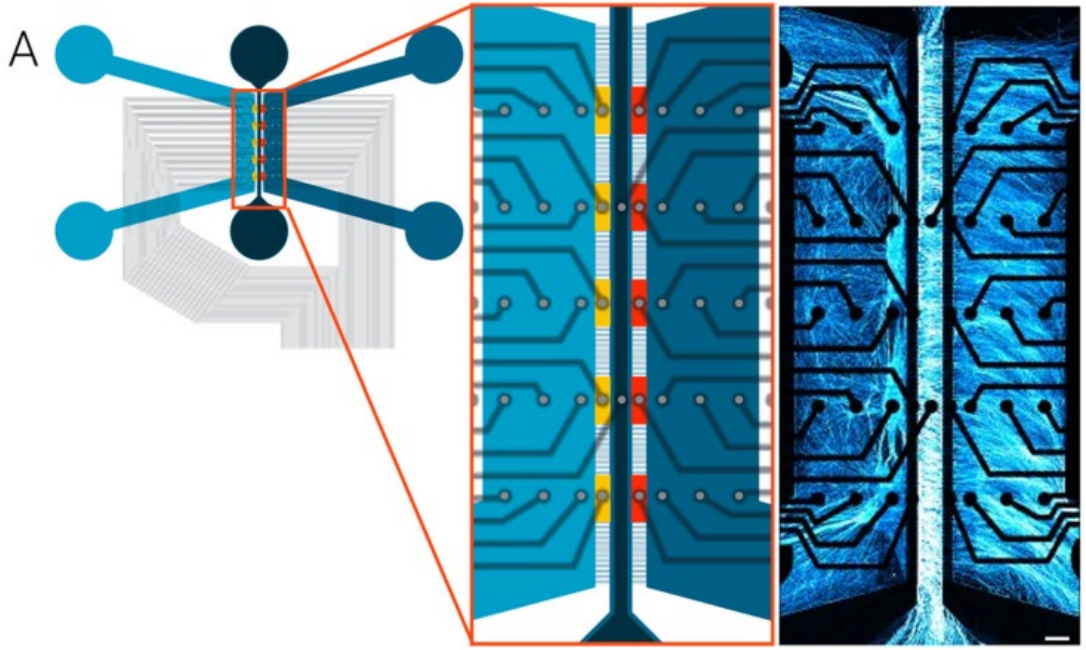
- DuaLink MEA compartmentalized device (microfluidic chip)
- NHEK / iPSC-sensory neuron co-culture
- MEA electrodes in microchannels
- ATP, lactic acid, KCl and temperature challenges

OVERVIEW

STUDY OBJECTIVE: BUILD A HUMAN, COMPARTMENTALIZED, ELECTROPHYSIOLOGY-ENABLED SENSORY SKIN MODEL

- DuaLink-MEA enables the selective stimulation of the axon terminal–keratinocyte interface
- Architecture: neuronal somas, microchannels and distal endings organized in separate fluidic compartments.
- Human iPSC-derived sensory neurons extend axons through microchannels toward keratinocytes.
- Treatments are applied to distal endings to better mimic peripheral exposure.
- MEA readout captures activity propagation through microchannel electrodes.
- Workflow: distal stimulation → axonal transduction → microchannel MEA signal → quantitative sensory response.

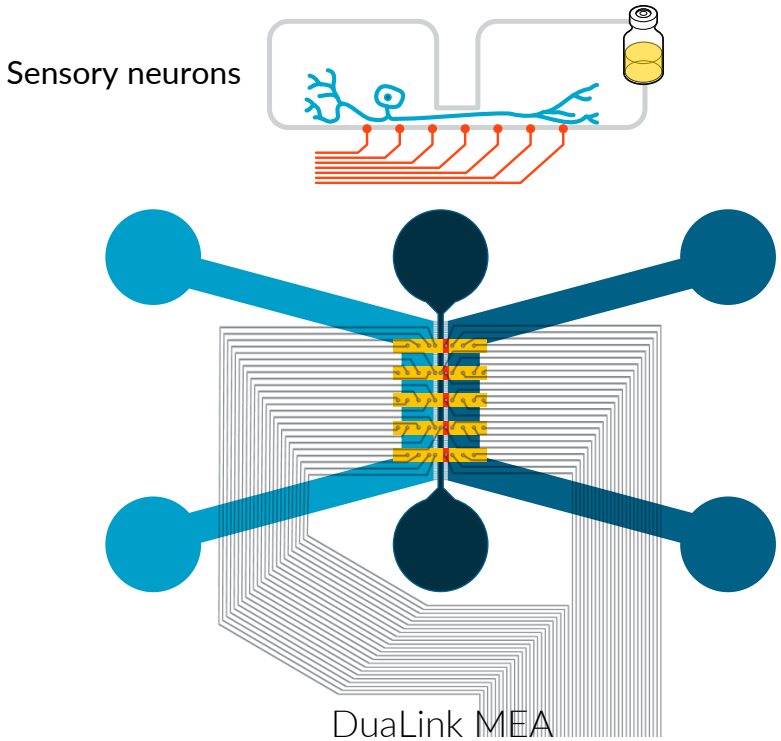


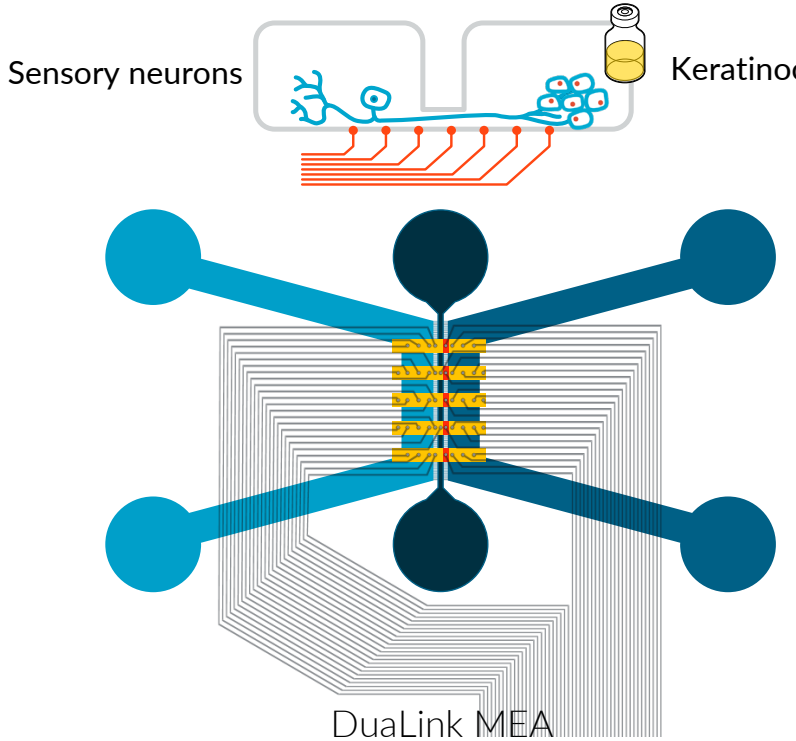


Compartmentalized device architecture and neurite growth after 21 days

SENSOR PLATFORM SELECTION

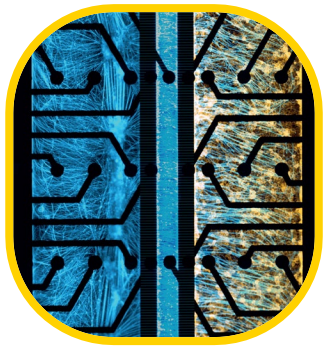
FROM SENSORY NEURON DIFFERENTIATION TO FUNCTIONAL CO-CULTURE STIMULATION





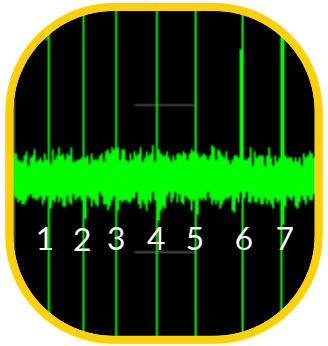
FUNCTIONAL READOUTS SELECTION

FUNCTIONAL ASSAYS: TARGETED STIMULATION + QUANTITATIVE ELECTROPHYSIOLOGY



Immunostaining

- βIII-tubulin,
- Nav1.7,
- TRPV1,TRPA1,
- P2X3,
- substance P,
- CK14
- Cx43,
- Synaptophysin



MEA Recording & Calcium Assays

- Spontaneous activity,
- Temperature challenge,
- Chemical stimulation at distal endings
- Fura-2 response of primary keratinocytes to ATP and lactic acid

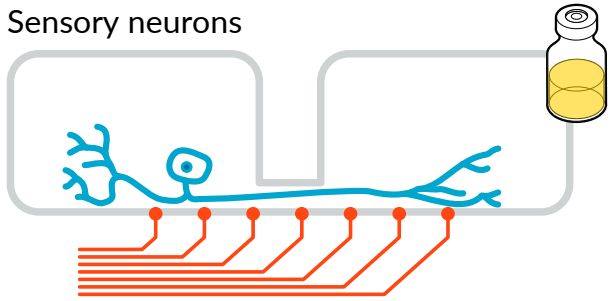
Readouts	Protocol	Biological question
Temperature challenge	37 °C baseline → 41 °C challenge → 37 °C recovery	Thermosensitive / TRPV-mediated neuronal responsiveness
Chemical stimulation	Vehicle → ATP 20 µM or lactic acid 0.3% → KCl 8 mM	Pruritogenic, acidic and depolarizing stimuli
MEA analysis	Spike detection according to two different protocols (NETRI) for acute and chronic effect analysis	Neuronal electrical activity in response to stimuli and keratinocytes responses
Calcium imaging	Fura-2 in keratinocytes; response every 6 s over 300 s	Keratinocyte direct responsiveness

- Key methodological advantage: the platform records afferent-like activity from microchannel electrodes while exposing only the peripheral endings.

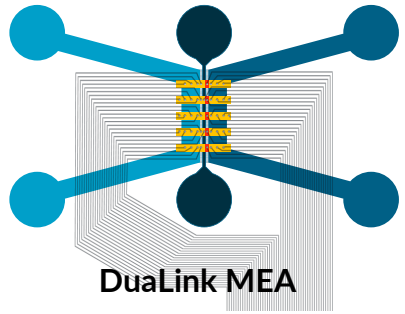
MICROCHANNELS AMPLIFY AND LOCALIZE THE ELECTROPHYSIOLOGICAL SIGNAL

- Spontaneous electrical activity was detected in all compartments.
- Microchannel electrodes recorded higher spike amplitudes than open channel electrodes.
- Microchannel geometry increases local resistance and constrains axons over electrodes.
- Subsequent analyses focused on microchannel electrodes, reflecting afferent signals from distal terminals toward somas.
- Why it matters: the device transforms axonal activity into a stronger, spatially defined extracellular readout.

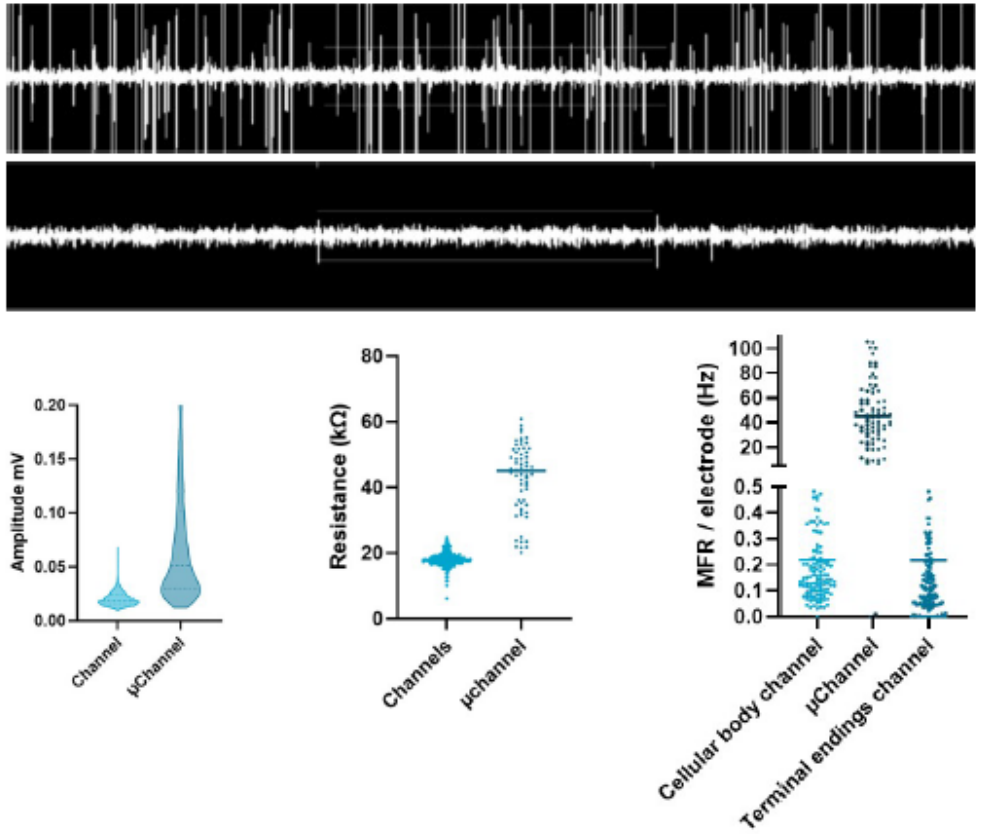
Diagram



Chip



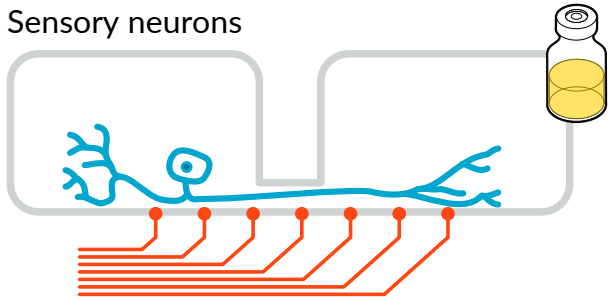
Illustrations



IPSC-DERIVED SENSORY NEURONS MATURE AND EXTEND AXONS IN THE MICROFLUIDIC CHIP

- After 21 days, neurons expressed nociceptor and sensory neuron markers.
- General sensory specification: BRN3A, Islet1, TrkA, NaV1.7, substance P.
- Ion channel / receptor repertoire: TRPV1, TRPA1 and P2X3.
- P2X3 and substance P staining support a mixed peptidergic / non-peptidergic phenotype.
- Axons reached the terminal compartment by day 9 and spanned it by day 17–21.
- Sensory neurons transduce temperature increase into electrical activity
- A global temperature challenge from 37 °C to 41 °C significantly increased spike frequency.
- 107 / 129 active electrodes showed >10% activity increase during the challenge.
- Response returned toward baseline during recovery at 37 °C.
- Functional interpretation: heat-sensitive neuronal activity consistent with TRPV channel functionality.

Diagram



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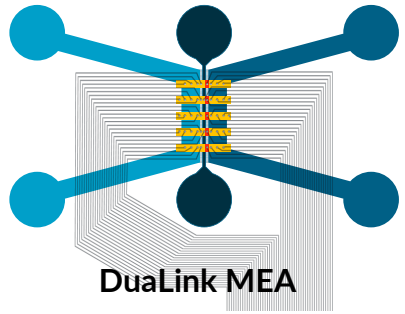
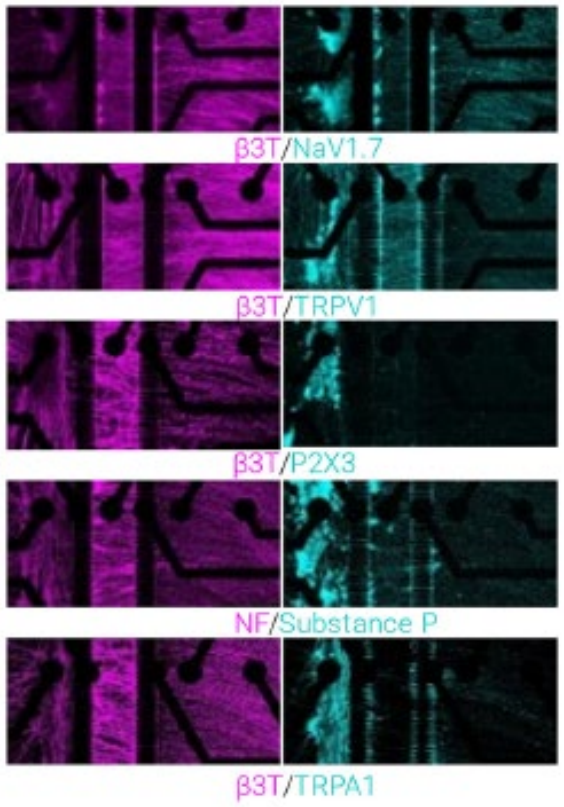
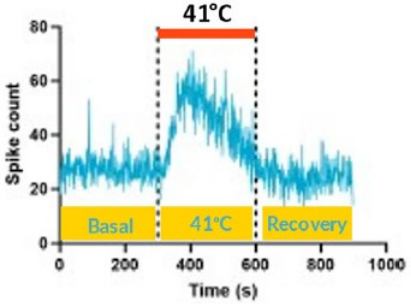
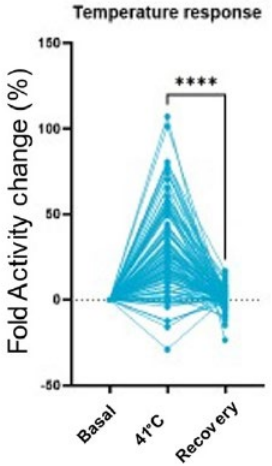


Immunofluorescence



MEA Temperature response

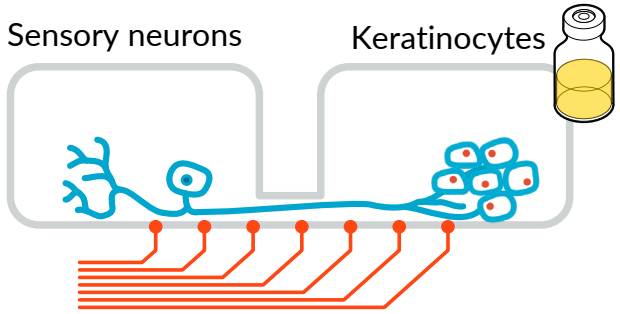




KERATINOCYTES EXPRESS SENSORY MARKERS AND PHYSICALLY INTERACT WITH NEURITES

- Primary human keratinocytes expressed CK14 and sensory-related receptors.
- Markers detected: TRPV1, TRPA1 and P2X3 (data not shown)
- In co-culture, neurites formed physical contacts with the keratinocyte layer.
- Connexin 43 puncta localized near neurites, suggesting possible interaction sites.
- Synaptophysin was detected in neuronal projections, not in keratinocytes at this imaging resolution.

Diagram



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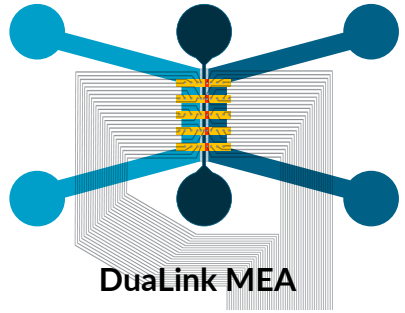
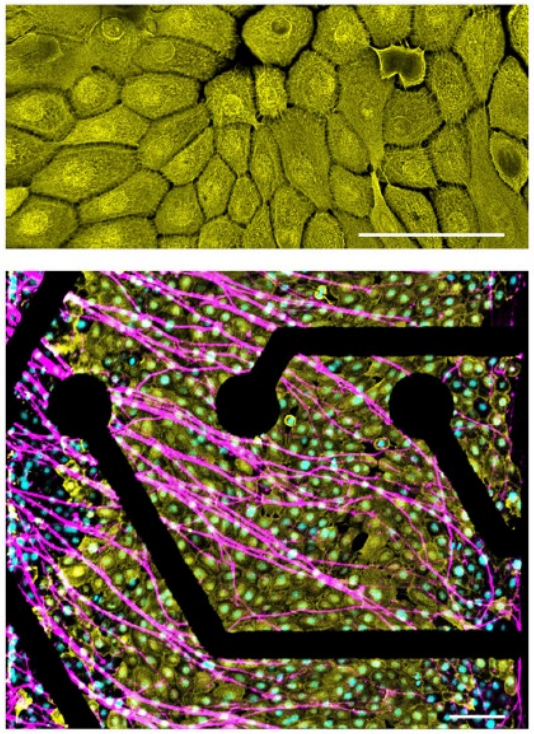
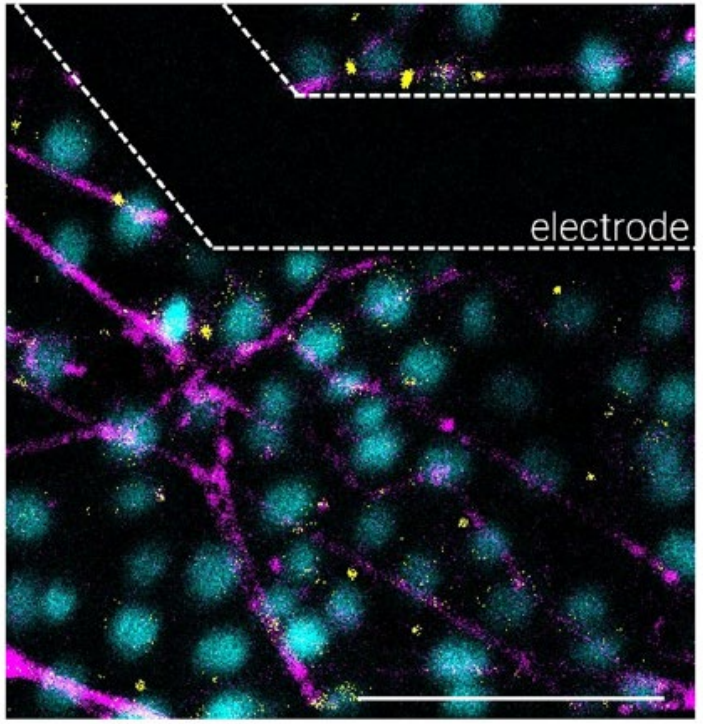


Immunofluorescence



βIIItubulin (magenta), CK14 (yellow), DAPI (cyan)
Scale bars: 100 µm.

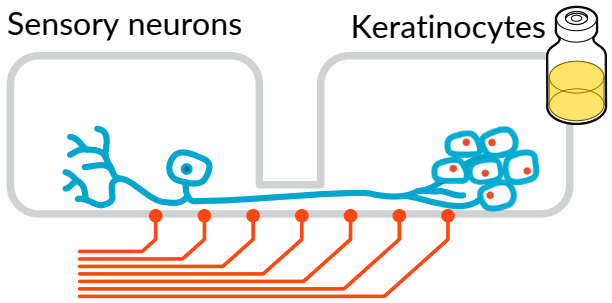


Synaptophysin (magenta), connexin 43 (yellow), and DAPI (cyan)
Scale bars: 100 µm.

KERATINOCYTES SUPPORT NEURITE REGROWTH AFTER AXOTOMY

- Neurite regrowth was almost absent in keratinocyte medium alone.
- Co-culture conditions enabled axon extension into the keratinocyte layer.
- With or without added growth factors, co-culture regrowth approached neuronal-medium conditions.
- Interpretation: keratinocytes may provide supportive cues, potentially including soluble neurotrophic factors.

Diagram



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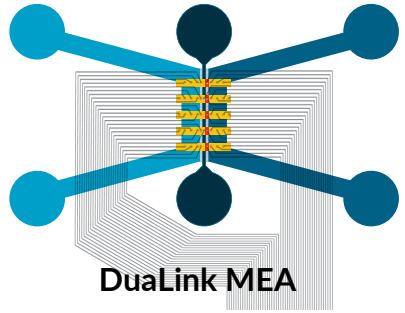
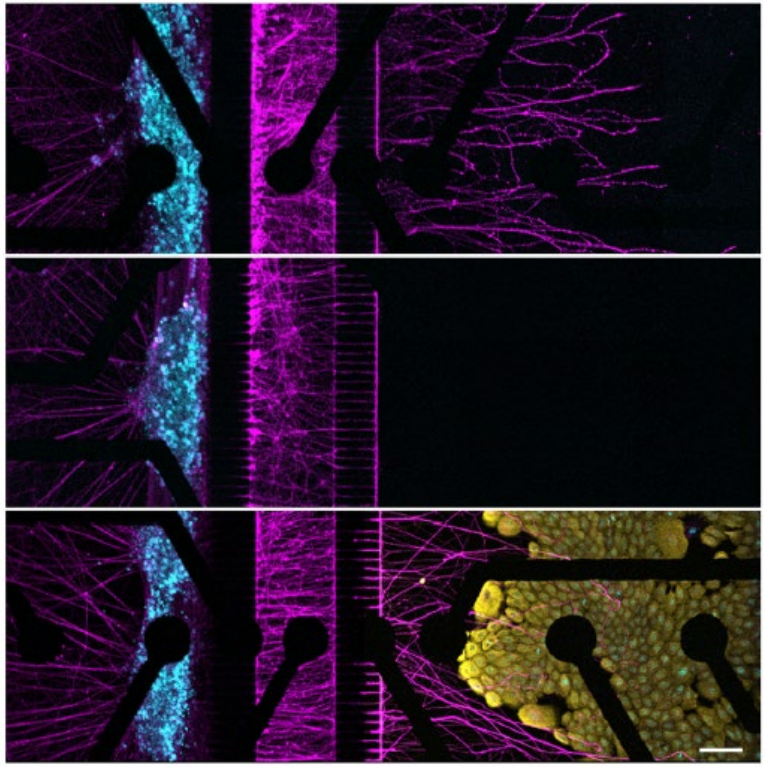


Illustrations



βIIItubulin (magenta), CK14 (yellow), DAPI (cyan)
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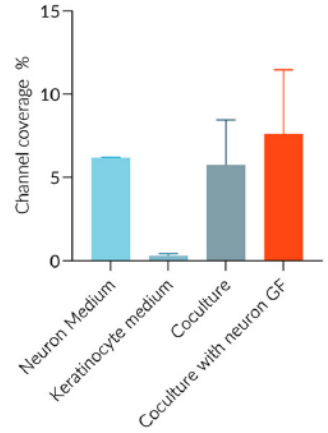
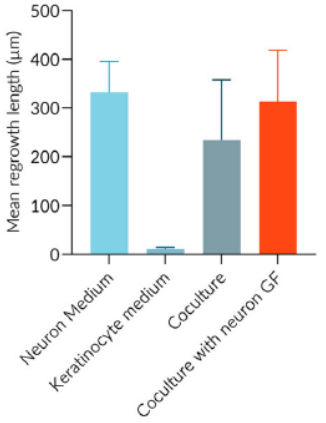




SELECTIVE DISTAL STIMULATION REVEALS ACUTE SENSORY RESPONSES

ATP 20 µM

- Pruritogen; activates purinergic receptors such as P2X3; involved in neuron–keratinocyte sensory transduction.

Lactic acid 0.3%

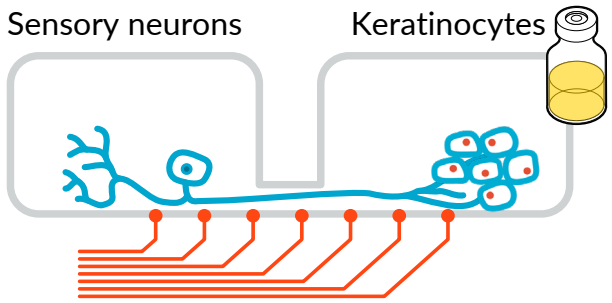
- Acidic stimulus associated with proton sensitivity and discomfort in sensitive or inflamed skin contexts.

KCL 8mM

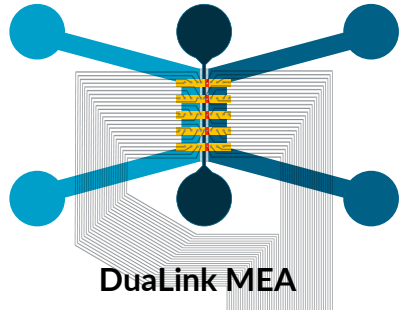
- Positive depolarizing stimulus used to confirm neuronal excitability.

- Neuron–keratinocyte co-cultures showed significant spike-frequency increases after ATP and lactic acid addition.
- Keratinocytes responded directly to ATP and lactic acid in Fura-2 calcium assays, indicating their possible participation in signal integration.
- The co-culture response profile is broadly consistent with that of neurons alone. (Data not shown)
- Subtle keratinocyte-mediated modulation of signal transduction may require patch-clamp or more specific molecular stimuli.

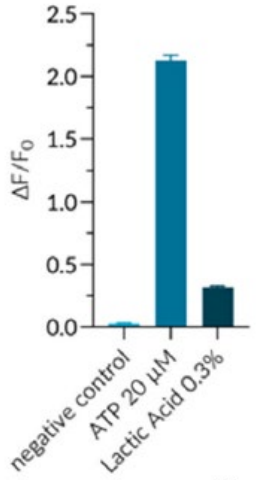
Diagram



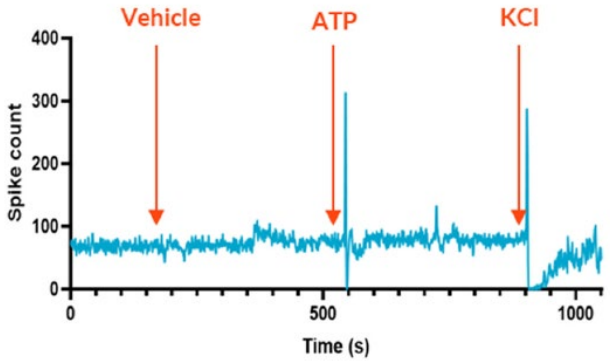
Chip

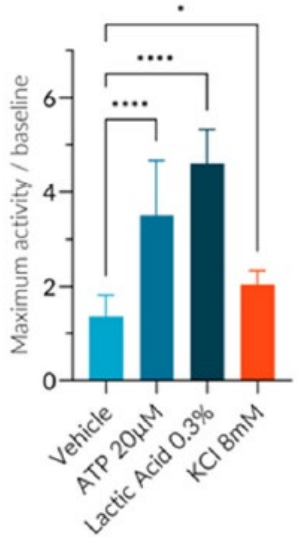


Calcium imaging _ keratinocytes



MEA Analysis _ Co-culture





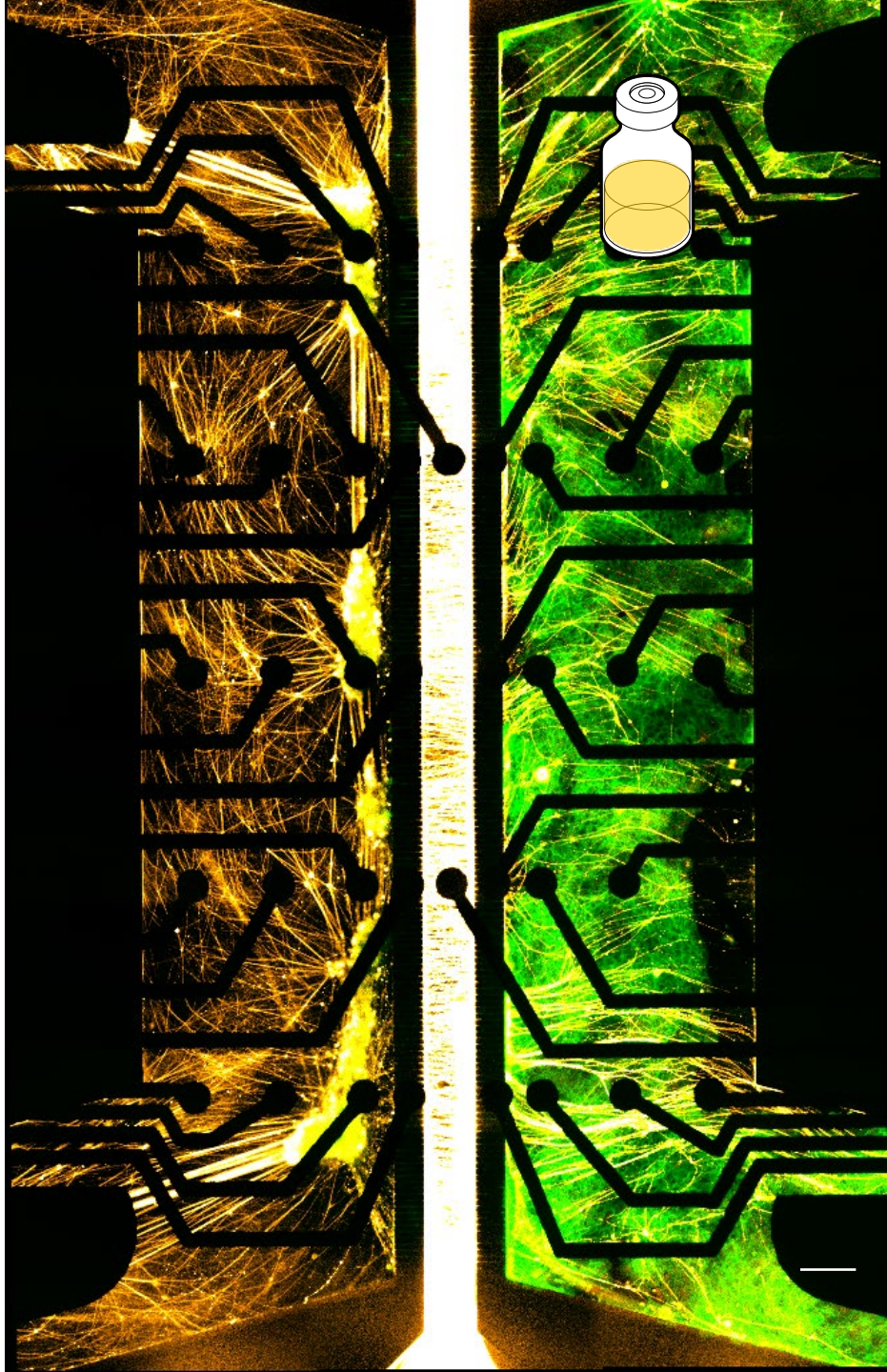
RESULTS

Established

- The model is validated as a functional innervated skin MPS; mechanistic dissection is next
- Microchannels improve axonal electrophysiological recording
- Human sensory neurons culture and maturation in a chip is robust
- Keratinocytes form a distal neurocutaneous interface
- Temperature, ATP and lactic acid evoke measurable MEA responses

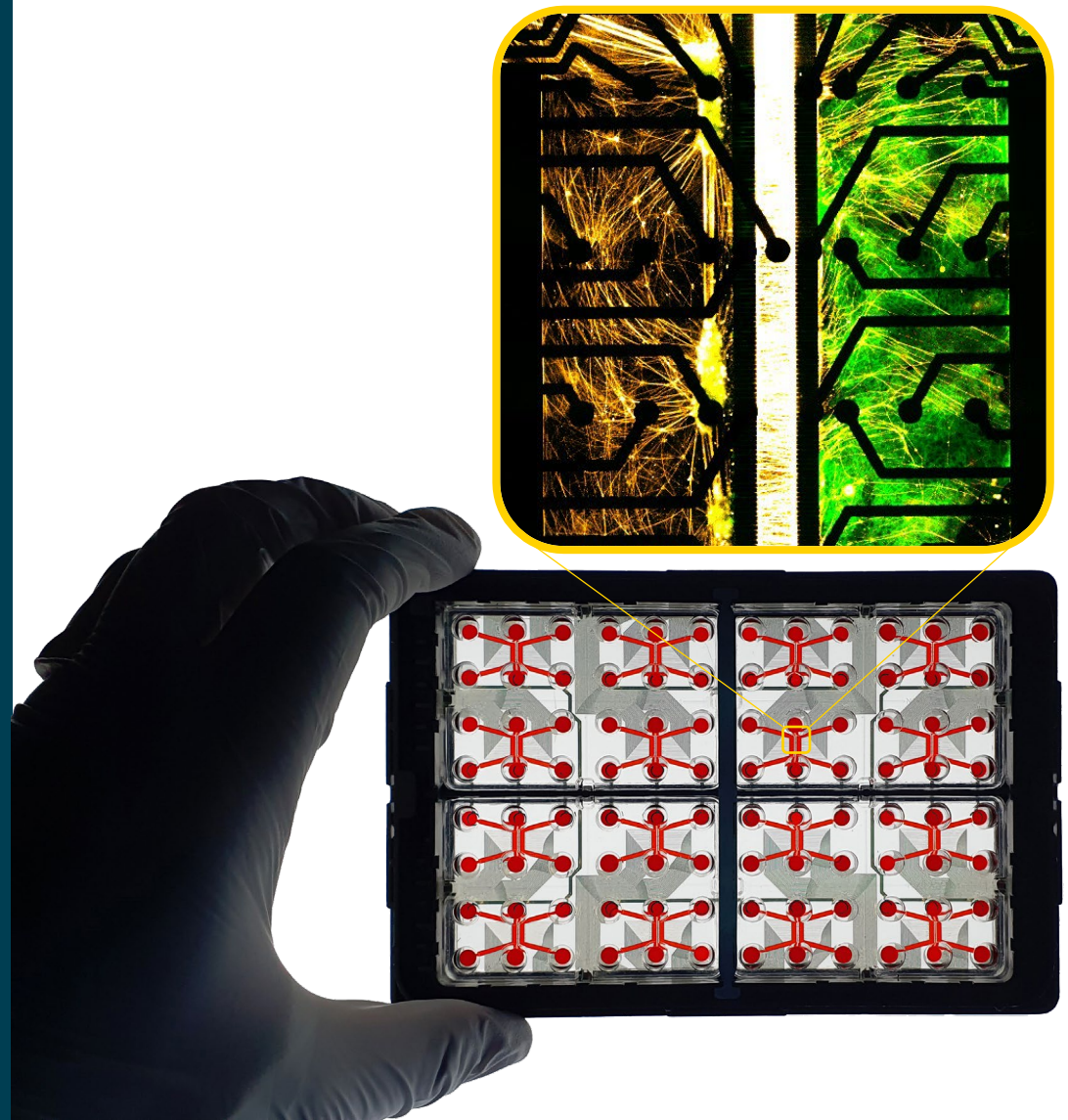
In optimization

- Whether keratinocytes amplify, dampen or reshape neuronal response kinetics
- Which communication route dominates: soluble factors, gap junctions, paracrine ATP, ion channels
- Whether disease or donor-specific keratinocytes alter sensory phenotypes



A HUMAN, FUNCTIONAL PLATFORM TO STUDY NEUROCUTANEOUS SENSORY BIOLOGY

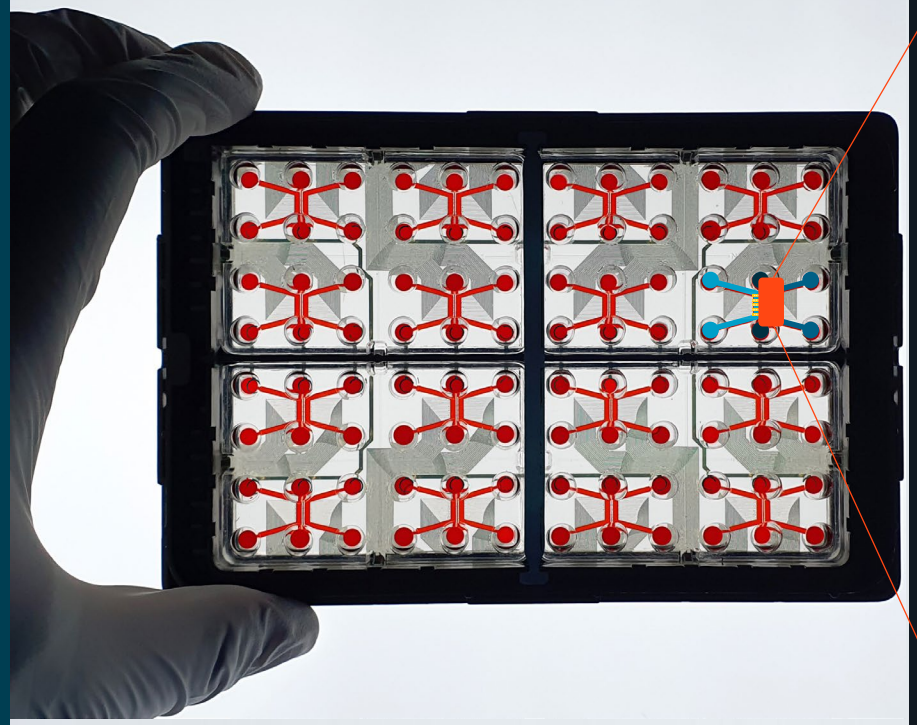
THE MODEL BRIDGES ARCHITECTURE, BIOLOGY AND QUANTITATIVE ELECTROPHYSIOLOGY

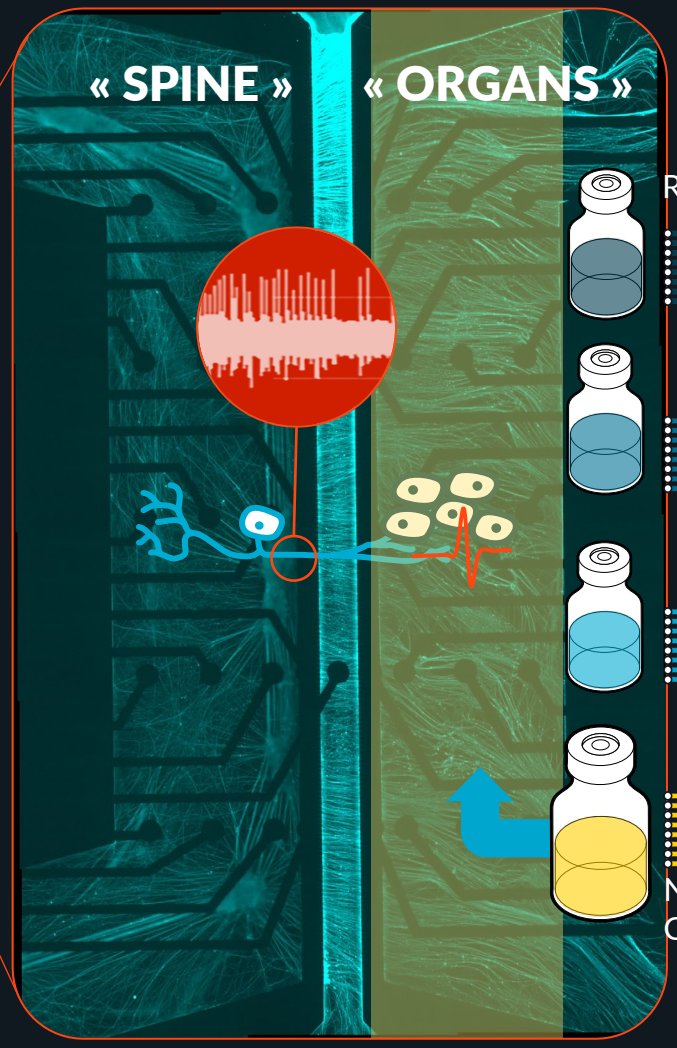


- Human relevance : iPSC-derived sensory neurons and primary keratinocytes capture key cellular components of skin sensation.
- Physiological organization : Compartmentalization separates soma and distal endings, enabling targeted peripheral stimulation.
- Functional readout : Integrated MEA provides real-time, non-invasive quantification of neuronal response to sensory stimuli.
- Screening potential : Parallel MEA-compatible format supports future compound testing for pain, itch, irritation and sensitive skin applications.
- Overall: DuaLink MEA enables selective stimulation of the axon terminal–keratinocyte complex and functional monitoring of sensory signal transmission.

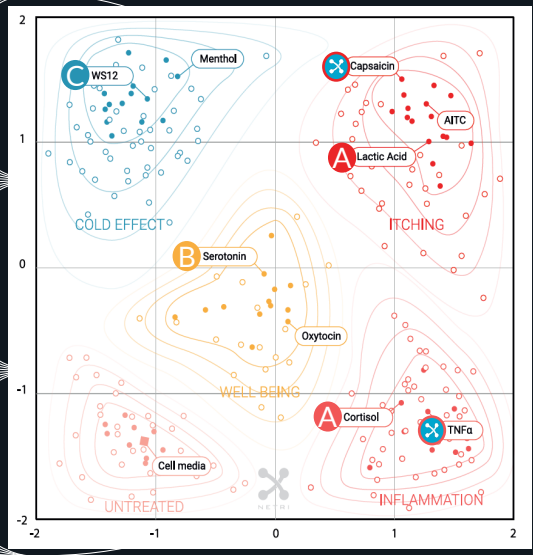
NEURON AS A SENSOR

A SUITE OF TOOLS FOR A UNIQUE SELLING PROPOSITION





References



New Compound

Neurons in our chips host a variety of dedicated receptors encoding a complex stimulus-response which can be deciphered to be specific

WO23187279,
WO23187280

Extracting 500+ Variables from electrophysiological signal into a digital signature…

… which is compared to a library of compounds and conditions to predict safety & efficacy, reduce attrition rates, development costs and animal use

ACKNOWLEDGEMENTS & REFERENCE

COLLABORATION ACROSS NETRI, EPISKIN AND L'ORÉAL RESEARCH & INNOVATION

- Study teams: NETRI and L'OREAL Advanced Research EPISKIN
- Co-first authors: Thomas Bessy and Anthony Martinez
- Corresponding author: Alexandre Guichard, NETRI, contact@netri.com
- All authors were employees of either EPISKIN or NETRI; no external funding agency grant was reported.
- Supplementary information includes device schematics, growth time course, marker panels, MEA characterization and keratinocyte calcium imaging.

Primary reference

Bessy T. et al. An in vitro organ-on-chip model for studying neuron–keratinocyte interactions in sensory response through electrophysiology. Lab on a Chip, 2026, 26, 248–256. DOI: 10.1039/d5lc00867k

An innovative platform offering a wide range of applications codeveloped by NETRI and EPISKIN/L'OREAL.

An *in vitro* organ-on-chip model for studying neuron–keratinocyte interactions in sensory response through electrophysiology

This study introduces a human-relevant in vitro model using iPSC-derived sensory neurons and keratinocytes in MEA-integrated microfluidic chips. Neurons expressed nociceptor markers, showed TRPV activity, and formed contacts with keratinocytes. Stimuli evoked electrophysiological responses, highlighting neuron–keratinocyte interactions relevant to pruritus, pain, and skin disorders, supporting therapeutic development.

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As featured in:

See Alexandre Guichard *et al.*, *Lab Chip*, 2026, **26**, 248.

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THE INDUSTRY ALLIANCE FOR MPS EUROPEAN PROVIDERS

IAMPS
Industry Alliance for Microphysiological Systems

A European Project

Our Nine Founding Members

AlveoliX · BiomimX THE BEATING ORGANS-ON-CHIP · chiron · DYNAMIC42 · insphero · MIMETAS · NETRI · REACT4LIFE mirroring human complexity · TISSUSE Emulating Human Biology

Unite the sector
Unite and represent companies across Europe developing microphysiological systems (MPS), such organs-on-chips, organoids, and other advanced human-relevant biological models;

Partner with stakeholders
Partner with other industry and public actors who share a common commitment to advancing human-centric science;

Contribute to EU Policies
Work with EU institutions and contribute to regulatory and science policies to ensure that MPS benefit patients, researchers, and society.

Advance the regulatory acceptance of MPS devices

- Focus on applications for **unmet needs**.
- Identify **Context of Use & endpoints** validation studies.
- Facilitate **interactions** between EMA, JRC and MPS developers (early dialogues).
- Facilitate access to **EU-based hiPSC**.

Foster strategic collaborations with end-users

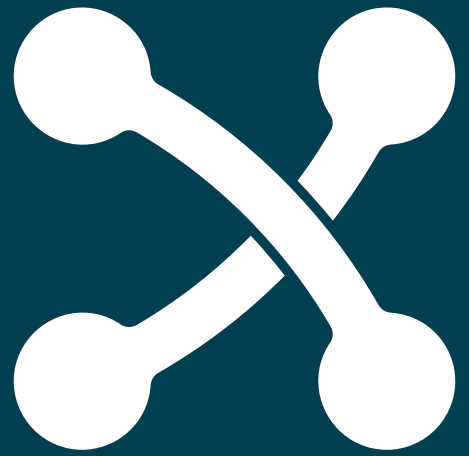
- Focus on applications for **unmet needs**.
- Identify **Context of Use & endpoints** validation studies.
- **Facilitate identification** of MPS EU technologies
- Promote MPS **complimentary technologies**.

contact@iamps.eu

THANK YOU

netri.com
contact@netri.com

BOOTH #618



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