NEURON-AS-A-SENSOR (NAAS) APPLICATIONS FOR IN VITRO MONITORING OF 3D TUMOR ORGANOID TREATMENT RESPONSES.

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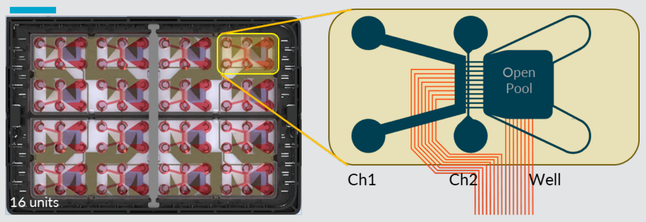
BACKGROUND



Advanced 3D tumour models, including patient-derived organoids, present major challenges for therapeutic response monitoring due to limited optical accessibility, high spatial heterogeneity, and the poor suitability of conventional endpoint assays.
Here, we introduce a neuro-integrated colorectal cancer (CRC) organoid platform based on a **Neuron-as-a-Sensor (NaaS)** concept, where sensory neurons function as living biological transducers that **detect tumour-derived signals and convert them into quantifiable electrophysiological signatures for dynamic, non-invasive monitoring of tumour responses**.
The platform consists of a compartmentalized microfluidic device incorporating a customized microelectrode array (MEA), designed to spatially organize co-cultures of patient-derived CRC organoids embedded in a neuro-conductive hybrid hydrogel and sensory neurons.

RESULTS

PD CRC ORGANOIDS ARE INNERVATED AND RESPOND TO ANTICANCER MONO/COMBINATION THERAPIES

PD CRC organoids were fully innervated in the well of Netri NB DuaLinkWell.

- Neurites of sensory neurons from channel 1 of the device extended to the well and innervated CRC oganoids.

Treatment efficacy in Transwells and Netri NB DuaLinkWell devices was similar.

- Anticancer monotherapy (20nM SN38 on days 1,4 for 2 weeks) and combination therapy (20nM SN38 on days 1,4 + 162nM ATMi on days 1-7 for 2 weeks), induced morphological changes onto PD CRC organoids. Combination therapy showed improved efficacy.

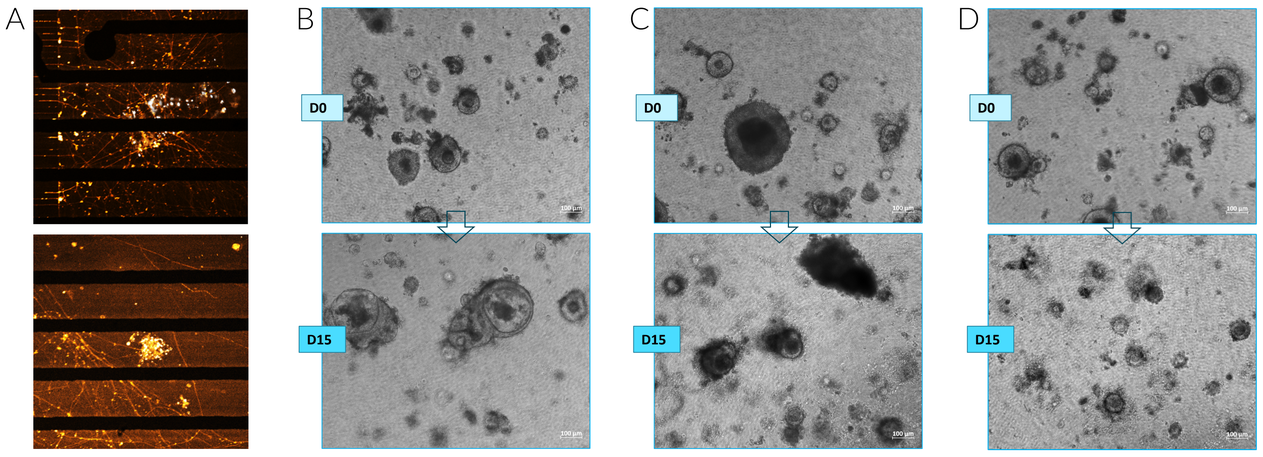


Fig. 1 PD CRC organoids innervation and response to anticancer therapies. (A) Innervated CRC organoids in NB DuaLinkWell devices (B) Untreated (control) PD CRC organoids; (B) PD CRC organoids following monotherapy (20nM SN38 on days 1,4 for 2 weeks) and (D) combination therapy (20nM SN38 on days 1,4 + 162nM ATMi on days 1-7 for 2 weeks). Treatment efficacy in Transwells and Netri NB DuaLinkWell devices was similar (data not shown).

MEA RECORDING, DATA ACQUISITION AND POST-PROCESSING

Following data recording using MaestroPro platform, data and over 40 metrics were extracted using a Netri developed software post-processing tool. Data were normalized by recordings at D10. Only representative metrics were investigated and statistically assessed, following Mixed effect with False Discovery Rate corrections.

Most representative recorded and processed metrics

- Mean firing rate (MFR)
- Burst frequency / duration
- Burst percentage / number of bursts
- Number of spikes per burst

Significant metrics augmentation for treated CRC-neuronal co-cultures compared to sensory neurons monoculture

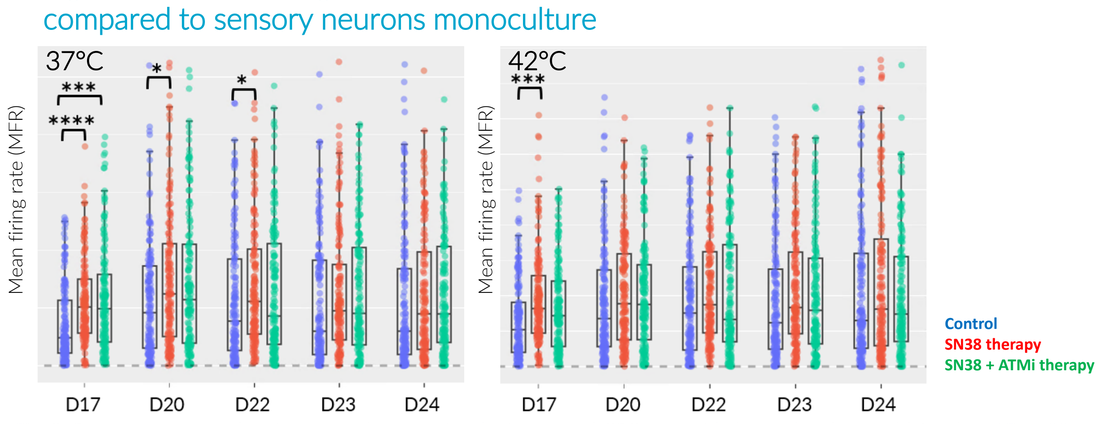


Fig. 2. Representative results of processed metrics for the innervated CRC organoids (treated and controls) for days 17 to 20 from the treatment and co-culture onset. Significant MFR increase mainly at D17 from the treatment onset.

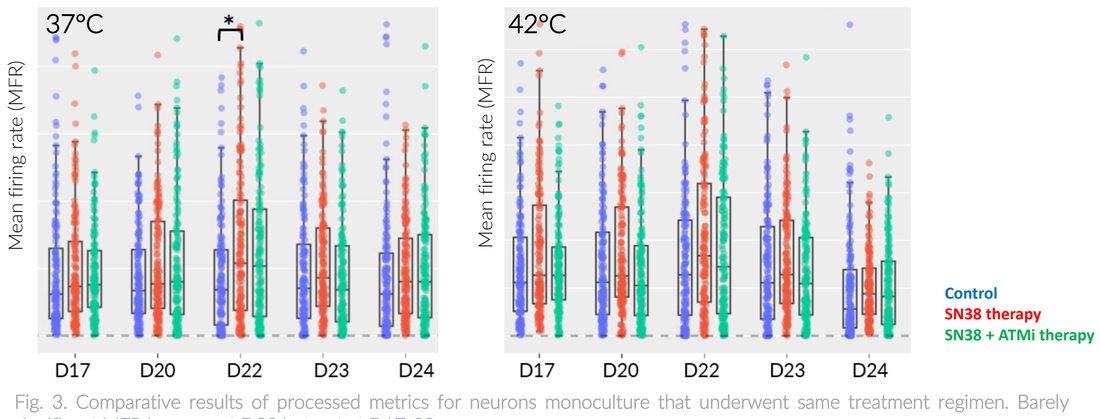


Fig. 3. Comparative results of processed metrics for neurons monoculture that underwent same treatment regimen. Barely significant MFR increase at D22 but not at D17-20.

REPRESENTATIVE METRICS ANALYSIS

Co-cultured sensory neurons and CRC organoids displayed different electrophysiological behaviour than treated sensory neurons monoculture.

	CO-CULTURE SENSORY NEURONS + CRC ORGANOIDS	MONOCULTURE SENSORY NEURONS
Most relevant metrics		
• Mean firing rate (MFR)	YES Significant differences (37°C/42°C), mainly at D17	FEW Significant differences (37°C/42°C)
• Burst percentage / number of bursts	NO No significant differences (37°C/42°C)	OUI différences significatives (42°C), 0 D17
Additional metrics:		
• Burst duration	YES Significant differences (37°C), at D17, D22	NO No significant differences (37°C/42°C)

Mechanistic hypothesis

Mechanistically, the recorded treatment efficacy is potentially due to TNFα production at patient derived CRC organoid level;

MFR increase can be induced by TNFα (200ng/mL) addition for 4h on sensory neurons + patient derived CRC organoids co-culture but not on neurons monoculture at 37°C.

At 42°C the reponse to TNFα is observed in neurons mono-culture only as in the co-culture, at D23, the neurons are displaying functional exhaustion.

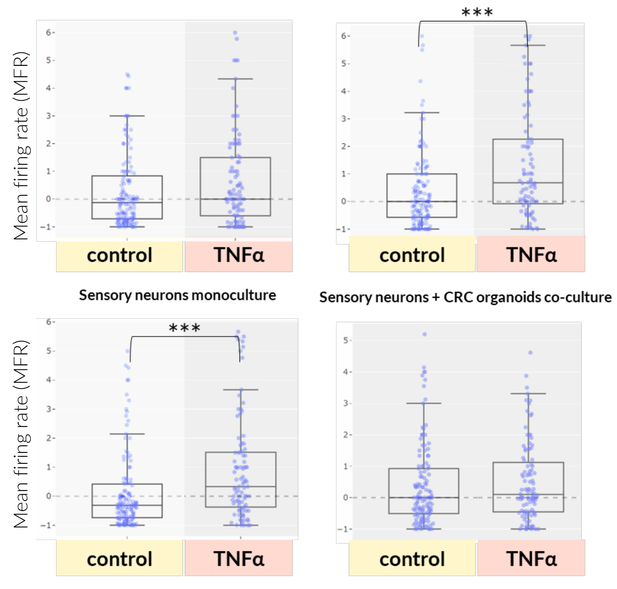


Fig. 4. TNFα positive control (200ng/mL) induces MFR increase at 37°C for therapy responsive neurons+CRC organoids at D23 from treatment onset. This suggests the electrophysiological response to treatment observes a cytokine based mechanism.

CONCLUSION & PERSPECTIVES

1. Sensory neurons and patient-derived CRC organoids are developing robust, spatially organized interactions in Netri NB DuaLinkWell devices, consistent with the formation of innervated tumour structures within defined device compartments.
2. Clinically relevant anti-CRC treatments, including monotherapy and combination therapy, with continuous monitorisation of neuronal activity as a functional readout of tumour response were successfully performed and documented.
3. Robust discrimination between treatment effects require observation of multiple electrophysiological metrics.
4. These findings suggest that treatment efficacy may be linked to a TNFα-mediated response originating from the CRC organoid compartment
5. As a perspective, method validation arises from correlating clusters of recorded and processed MEA metrics and clusters of cytokines generated during the anti-cancer therapies.

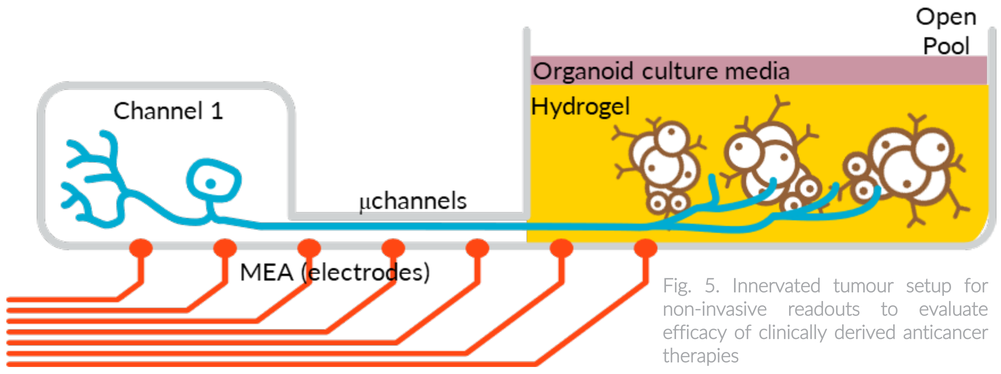


Fig. 5. Innervated tumour setup for non-invasive readouts to evaluate efficacy of clinically derived anticancer therapies

- In summary, this work demonstrates the feasibility and value of a neuron-as-a-sensor strategy for label-free, real-time monitoring of therapeutic responses in complex 3D tumour models.
- Integrating patient-derived CRC organoids with neuronal biosensors in a microfluidic MEA platform offers a scalable and functionally relevant strategy to improve preclinical drug testing and translational cancer modelling.

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