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JOINT EVENT

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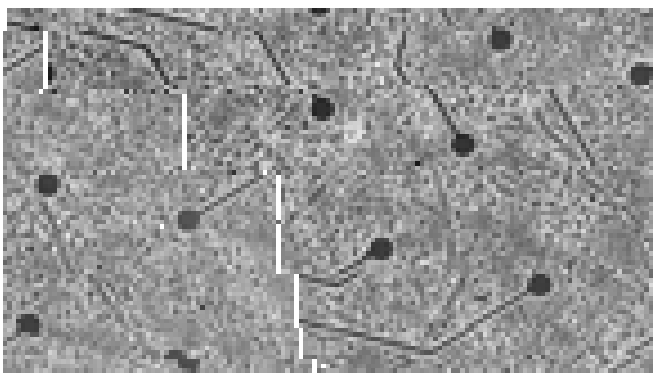
Statement of the Problem: In accordance with 3Rs, alternative models are required to replace standard neurotoxicity testing. High-content, high-throughput tools are needed considering speci c features of nervous system (NS) functioning to identify neurotoxic vs. cytotoxic e ects. By considering intercellular communication through transmitters and transmitter sensors (receptors), and collective behavior of neuron network as relevant NS functional features, the purpose of this study is to develop tools providing neuron-speci c endpoints.

Methodology & eoretical Orientation: A multi-disciplinary electrophysiological, neurochemical and immunocytochemical approach, combining electrical activity recording of neuron network (on engineered micro-electrode arrays (MEAs) equipped with 60 electrodes onto which cerebrocortical neurons were cultured; data analysis through a home-made so ware and measurement c transmitter release was used to assess network maturation and to detect e ectiveness of neuroactive/neurotoxic substances.

Findings: During network development, maturation of glutamatergic/GABAergic neuron networks, target for relevant neurotoxicity mechanisms (excitotoxicity) and drugs classes, was observed. In mature networks, synaptic connectivity was related to activatio of glutamatergic pathways, and the system behaved as a sensitive sensor of glutamatergic transmission functioning. Activation c blockade of NMDA/AMPA receptors, or blockade of glutamate transporters, induced ring and bursting activity variations related to the e ects on transmitter release. Also, the network sensed the ne transmission variations involved in synapse plasticity: the collective network behavior and glutamate release were controlled by NMDA-dependent NO-cGMP pathway, as indicated by its pharmacological manipulation (NO synthase/guanylyl cyclase inhibitors, NO donors/8Br-cGMP). By presenting examples of network activity modulation by neuroactive substances (glutamate/GABA receptor agonists/antagonists) and by known neurotoxicants (e.g., domoic acid, chlorpyrifos oxon), and ine ectiveness of molecules not exhibiting acute neurotoxic e ects, we report evidence that MEAs-coupled neuron networks can represent an integrated approach for neurotoxicity testing based on functional neuron-speci c endpoints. ey might provide an e ective in vitro alternative tool for evaluating substance neurotoxicity, also providing a mechanistic approach.



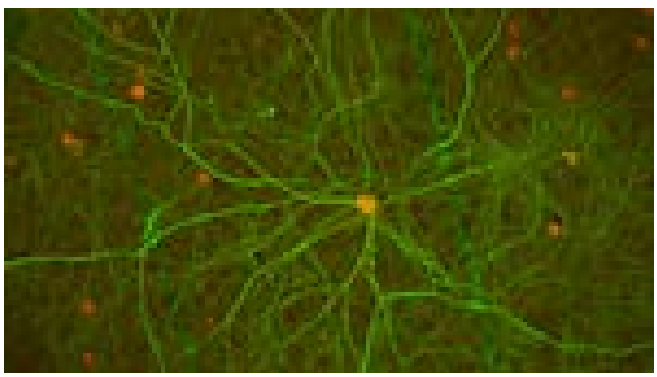


Figure 1: Neuron network on MEAs; primary rat cerebrocortical neuron cultures from E19, 24 DIV. The network on microelectrode arrays is shown. Immunocytochemistry for MAP2 (green) and NeuN (red).

Recent Publications

1. Frega M, Pasquale V, Tedesco M, Marcoli M, Contestabile A, et al. (2012) Cortical cultures coupled to micro-electrode arrays: a novel approach to perform in vitro excitotoxicity testing. Neurotoxicol Teratol 34:116–127.
2. Marcoli M, Agnati L F, Benedetti F, Genedani S, Guidolin D, et al. (2015) On the role of the extracellular space on the holistic behaviour of the brain. Rev Neurosci 26(5):489–506.
3. Fuxe J, Agnati L F, Marcoli M and Borroto-Escuela D (2015) Volume transmission in central dopamine and noradrenaline neurons ant its astroglial target. Neurochem Res 40(12):2600–14.
4. Cervetto C, Vergani L, Passalacqua M, Ragazzoni M, Venturini A, et al. (2016) Astrocyte-dependent vulnerability to excitotoxicity in spermine oxidase overexpressing mouse. Neuromolecular Med 18:50–68.
5. Pietropaoli S, Leonetti A, Cervetto C, Venturini A, Mastrantonio R, et al. (2018) Glutamate excitotoxicity linked to spermine oxidase overexpression. Mol Neurobiol. 55(9):7259–7270.

Biography

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