

Alzheimer's disease (AD) *in-vitro* model: a novel drug screening approach with large-scale high-density microelectrode array

Hayder Amin^{1,*}, Alessandro Maccione¹ and Luca Berdondini¹

¹ Istituto Italiano di Tecnologia (IIT), Neuroscience and Brain Technology Department – Genova, Italy

* Corresponding author: hayder.amin@iit.it

ABSTRACT

A known major limitation in the pharmacological R&D for AD is the missing understanding of the real causes of the pathology. Current research is mainly focused on the different factors involved in the development of the disease, including inflammation, oxidative damage, and cytoskeletal abnormalities. However, progress in this research is also slow down by the absence of reliable *in-vitro* methodologies to complement *in-vivo* experiments on animal models. Here we investigate an approach based on high-resolution electrical read-outs from neuronal cultures that might contribute in accelerating the study of the pathology as well as for testing the effects of different molecular entities.

Over past years the main hypothesis in AD research is based on the involvement of the amyloid cascade¹. Many studies strongly suggested that soluble oligomers of amyloid beta (A β 1-42) cause functional toxicity in neurons, by inhibiting the neuronal spontaneous activity without significant cell death at nanomolar concentration^{2,3}. This toxicity causes specific aberrations in synaptic signaling leading to synapse degeneration by a considerable amount of time. In this context, at first, we recorded pathologically-induced functional effects in wild-type neuronal cell cultures. Our preliminary results acquired from rat hippocampal neural populations cultivated on the surface of a novel generation of High Density Microelectrode array (HD-MEA)⁴ devices (4096 electrodes, electrode size 21 μ m, spatial density \sim 580 electrode/mm² and full array recordings at sampling rate of 7.7 KHz/electrode) show that the spontaneous spiking activity is reduced with application of A β at 100 nM concentration. Secondly, we investigated the effects of a drug in rescuing the spontaneous activity. In particular, we achieved the reversal of the A β induced functional deficit in the spontaneous activity by applying Memantine, a drug that interact significantly with A β and reverse its toxicity effect.

Uniquely, these results show that this non-invasive long term electrical read-out approach increases the recording throughput in terms of target cell simultaneously probed in large-scale neuronal networks and that it can be applied for AD research *in-vitro*. Based on these results, our overall aim is to standardize and optimize the experimental and analysis tools for target-based screening assay.

As a perspective, functionalized HD-MEA with 3D platinum electrodes fabricated by beam-induced deposition (IBID) technique⁵ reminiscent of mushroom-shaped protruding gold spine⁶ might provide intracellular like signal quality⁷. Additionally, human induced pluripotent stem (hiPS) cells can be differentiated into neuron⁸ and pave the way to the use of *in-vitro* human cell culture models for drug research. The use of our high-resolution electrical read-out approach with human cell culture models for drug screening assay might be an effective approach to mitigate the potential risks of translating pre-clinical outcomes into clinical trials.

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