Title: **Human brain organoids – breakthrough towards modelling and treatment of neural disorders**

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Abstract:

The ability of pluripotent stem cells to self-organize under 3D *in vitro* culture conditions into highly structured tissue patterns, opened the era of "brain organoids". This technological advancement based on human induced pluripotent stem cells (hiPSC), obtained by reprograming of somatic cells, enabled researchers to model human neurodevelopment and neuropathology in *in vitro* conditions with the challenge owing the lack of available animal models and ethical considerations. In addition brain organoids derived from patient-specific hiPSC, while modelling disease, can be also personalized for diagnostic or therapeutic purposes.

While brain organoid system appeared feasible to model early neurodevelopment and its pathology, it has anatomical and functional limitations to study later developmental stages due to the lack of the correct neuronal network connectivity and vascularization. Much work in the field has been addressed to overcome this limitations with two parallel, but interdependent, directions: the first is focused on developing new protocols to generate replicas of multiple brain regions, while the other is based on constricting regulatory control of the system through bioengineering approaches. The latter include gene editing and optogenetic technology as well as strategy to upgrade the physiological relevance of the system with microfluidic "organ on the chip" devices. Last but not least are developments in new technologies for unbiased organoid analysis.

This report will focus on state of the art regarding modelling *in vitro* of neurological disorders to underline the advantage of specific type of organoids (cerebral, "self-patterned" versus brain region specific "patterned") for particular brain pathology. The possibility for upgrading of physiological relevance of brain organoids will be also discussed.

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