COnNect - Engineering human cortical brain organoid's connections to restore brain functions

Brain injuries affecting the cerebral cortex result in devastating neurologic deficits from irreversible loss of neurons and still do not have any therapeutic option. The only possible treatment for these conditions would be the reconstruction of the lost neuronal circuits which could be achieved, in principle, by stem cell therapy. However, when stem cells are engrafted they only provide trophic effect and are incapable of substantial tissue replacement and rewiring the damaged tissue. With this project I aim at implementing a paradigm shift toward a new targeted therapeutic approach enabling restoration of functional neuronal network activity in cortical brain lesions. In this view, I aim at: i) Developing a human-specific hydrogel able to support cortical brain organoids (CBOs) engraftment; ii) Achieving in vitro guidance of functional neuronal connections between CBOs via 3 dimension (3D) bioprinting; iii) Connecting CBO and lesioned mouse visual cortex using intravital 3D bioprinting; iv) Achieving in vivo functional network restoration via guided CBO integration within the lesioned cortex circuit. I already developed in vivo fabrication of customized 3D hydrogels by 2-photon mediated crosslinking of photo-sensitive polymers in cortical brain of living mice adjacent to implanted CBOs, able to guide CBO's growth in vivo. The ground-breaking nature of COnNect lays on the novel idea of i) creating in situ extra cellular matrix (ECM) mimic structures to re-establish in vivo the neuronal network and the lost neurological functions; ii) using brain organoids as an electrically active unit with defined organized structure to stimulate brain plasticity and reinforce synaptic connections with the host brain tissue. The proposed project has the potential to provide a new beyond state-of-the-art therapeutic option for cortical brain lesion therapy only possible combining multiple competences belonging to different fields: neuroscience, cell therapy, bioengineering.

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