Authors response to the Journal Club article « Delayed Heterochronic Transplantation following Focal Cortical Lesion Improves Outcome» by Vanessa Donega (2017)

Authors list and affiliations:
Péron S[1,2], Droguerre M[1,2], Debarbieux F[3,4], Ballout N[1,2], Benoit-Marand M[1,2], Francheteau M[1,2], Brot S[1,2], Rougon G[3,4], Jaber M[1,2,5], Gaillard A[6,2].

1. INSERM U1084, Experimental and Clinical Neurosciences Laboratory, Cellular Therapies in Brain Diseases Group, University of Poitiers, 86022 Poitiers Cedex, France.
2. Université de Poitiers, U1084, 86073 Poitiers Cedex, France.
3. CNRS, UMR 7289, ImaPath, Institut de Neurosciences de la Timone, Faculté de Médecine, 13005 Marseille, France.
4. Aix-Marseille Université, 13284 Marseille Cedex 07, France, and.
5. CHU de Poitiers, 86021 Poitiers Cedex, France.
6. INSERM U1084, Experimental and Clinical Neurosciences Laboratory, Cellular Therapies in Brain Diseases Group, University of Poitiers, 86022 Poitiers Cedex, France, afsaneh.gaillard@univ-poitiers.fr.

We thank Dr. Donega for her inspired review of our study (Péron et al., 2017). In the quest for the mechanisms underlying the benefits of delayed transplantation of neuronal progenitors in the injured cerebral cortex, she indeed rightfully emphasizes the potential role of inflammation. Follow-up work from our laboratory specifically suggests that inflammatory response to injury and levels of a specific interleukin are at least in part responsible for the observed improved integration of delayed grafts (unpublished observations).

As mentioned by Vanessa Donega, one of the striking findings in our study is that delaying grafting changes graft-host interactions, particularly that of the vascular network. In line with her proposal, further studies are underway aiming to better understand graft-host interactions at various levels such as cellular migration, vascularization, and neuronal connectivity. Interestingly, while our work demonstrates that grafted cells develop efferent connections to appropriate cortical targets, the use of rabies virus-mediated retrograde trans-synaptic tracing recently allowed the demonstration that grafted cortical embryonic neurons receive connections from endogenous neurons following a similarly specific pattern (Falkner et al., 2016).

Donega proposes to determine whether delaying transplantation also improved cortical layer formation within the graft. We have previously reported the absence of laminar organization within the transplant and have shown that the grafted neurons are rather organized into distinct clusters expressing specific cortical layer markers (Ballout et al., 2016). Unpublished observations suggest that delaying transplantation does not modify this organization.

Finally, Vanessa Donega appropriately concluded that our findings, based on the well-described model of embryonic neuron transplantation, would be of clinical relevance once the optimal neuronal source for transplantation has been found. While our work shows that a one-week delay is optimal for neuronal transplantation of

cortical progenitors in the lesioned mouse brain, future work should also focus on defining the optimal time-window for transplantation in a human context. A specie-specific temporal response to injury may be reasonable to expect, in consonance with the previously described protracted development of human stem cell-derived neuronal progenitors as compared to their mouse counterparts when transplanted in the mouse brain (Espuny-Camacho et al., 2013).

The recent advances in the field of human brain modelling demonstrated the possibility of generating 3D brain-like structures *in vitro* from human pluripotent stem cells (Lancaster et al., 2013) and iPSCs-derived functional microglia transplantable in the mouse brain or in human organoids (Abud et al., 2017), thus providing valuable tools to study the lesion-induced inflammatory response of human cells.

References:

Abud EM, Ramirez RN, Martinez ES, Healy LM, Nguyen CHH, Newman SA, Yeromin AV, Scarfone VM, Marsh SE, Fimbres C, Caraway CA, Fote GM, Madany AM, Agrawal A, Kayed R, Gylys KH, Cahalan MD, Cummings BJ, Antel JP, Mortazavi A, Carson MJ, Poon WW, Blurton-Jones M (2017). iPSC-derived human mivroglia-like cells to study neurological diseases. Neuron 94: 278-293.

Ballout N, Frappé I, Péron S, Jaber M, Zibara K, Gaillard A. Development and Maturation of Embryonic Cortical Neurons Grafted into the Damaged Adult Motor Cortex. Front Neural Circuits. 2016 Aug 3;10:55.

Espuny-Camacho, Micheslsen KA, Gall D, Linaro D, Hasche A, Bonnefont J, Bali C, Orduz D, Bilheu A, Herpoel A, Lambert N, Gaspard N, Péron S, Schiffmann SN, Giugliano M, Gaillard A, Vanderhaeghen P (2013). Pyramidal neurons derived from human pluripotent stem cells integrate efficiently into mouse brain circuits in vivo. Neuron 77: 440-456.

Falkner S, Grade S, Dimou L, Conzelmann KK, Bonhoeffer T, Götz M, Hubener M (2016). Transplanted embryonic neurons integrate into adult neocortical circuits. Nature 10: 248–253.

Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, Homfray T, Penninger JM, Jackson AP, Knoblich JA (2013). Cerebral organoids model human brain development and microcephaly. Nature 501: 373-379.