



# Centre de Neurosciences Psychiatriques

## CNP SEMINAR

### ANNOUNCEMENT

Friday, April 28<sup>th</sup>, 2023 11:00 – 12:00

### Elucidating the mechanisms of neurodevelopmental and neurodegenerative diseases using *in vivo*-like human stem cell models

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Animal models are the current gold standard in disease modeling, however, successful phenotypic reversal of symptoms is often not replicated in human studies, likely due to differences in the physiology of human and murine cells. This highlights the need for human cell-based systems. Cell culture conditions fail to fully recapitulate the morphological and functional characteristics of human brain cells. A new system partially overcomes these limitations by transplanting human brain cells into the mouse brain and allowing them to differentiate and mature in an *in vivo* context. Human induced pluripotent stem cell (iPSC)-derived microglia transplanted into the mouse brain assume a primary human microglia-like state, with key aspects of human microglial gene expression that cannot be recapitulated in culture. Additionally, human neurons transplanted into the mouse brain display morphological and functional characteristics that resemble neurons found in the human brain more closely than *in vitro* models.

I have successfully used these transplantation models to model Fragile X syndrome (FXS) and familial Parkinson's disease (fPD). To model FXS, I transplanted neural precursor cells derived from FXS patient iPSCs and isogenic controls where the *FMR1* promoter was reactivated into the brain of mice. I showed that *FMR1* reexpression was maintained *in vivo* in edited cells, up until six months post-injection. I showed a new neuronal maturation phenotype in FXS, and my results suggested synaptic hyperactivity of FXS transplanted neurons, in line with previously published *in vitro* experiments. Additionally, I am currently assessing the dysfunction of microglia in fPD using the transplantation of human pluripotent stem cell-derived myeloid precursors carrying the alpha-synuclein A53T mutation and isogenic controls, where the mutation was corrected, in the brain of immune-deprived mice, and in brain organoid slices.

Invited by [nicolas.toni@chuv.ch](mailto:nicolas.toni@chuv.ch)

Publication:

M. Krzisch, H. Wu, B. Yuan, T. W. Whitfield, X. S. Liu, Dongdong Fu, J. Shih, C. M. Garrett-Engele, A. S. Khalil, T. Lungjangwa, A. N. Chang, S. Warren, A. Cacace, K. R. Andrykovich, R. G. J. Rietjens, B. Jain, O. Wallace, M. Sur, R. Jaenisch Fragile X syndrome patient-derived neurons developing in the mouse brain show *FMR1* -dependent phenotypes; *Biological Psychiatry*, January 1 2023  
<https://www.sciencedirect.com/science/article/abs/pii/S0006322322015293>

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Link for videoconference

<https://chuv.webex.com/chuv/j.php?MTID=mc712953d8b41f608d4eb904bfa06c279>