LIST OF PROJECTS (2)

PHD for MD SCHOLARSHIPS

FEBRUARY 2022

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PROJECT MD1

Title : Repairing peripheral Nerves with ExtracellulaR VesiclES (NERVES)

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State of the art

Despite surgical improvements, peripheral nerve (PN) injuries have a poor prognosis and functional recovery remains a challenge. The NOSE team has shown the efficacy of adult nasal olfactory ectomesenchymal stem cells (OSC) in nerve regeneration. But due to the time delay associated with culture, autologous stem cell transplantation cannot be performed during the acute phase of the injury and heterologous transplantation requires the use of immunosuppressants. The therapeutic benefit of stem cells relates to the trophic and immune factors they secrete via their extracellular vesicles (EV). These latter allow to develop new cell-free therapies to overcome cells limitations. EV are formed by a lipid bilayer and contain numerous molecules (proteins, lipids, mRNAs, miRNAs, lncRNAs, DNA) that play a key role in intercellular communication to promote neo angiogenesis, neuro-regeneration, myelination, axogenesis and immunomodulation, that induce beneficial effects on PN regeneration.

Objectives

The project will evaluate the therapeutic potential of EV derived from olfactory stem cells (OSC-EV) in PN regeneration with two main objectives. 1/ In vitro, the cellular processes involve in nerve repair will be identified using a 3D-nerve model and 2/ in vivo, the effectiveness of OSC-EV in the regeneration of rat peroneal nerve will be evaluated.

Methods

The 3D-nerve model will be based on a co-culture of Schwann cells from a primary culture and human neurons from IPSC in a matrix of silicone and Matrigel. The axonal growth and the myelination with and without EV will be evaluated. This model will be used to study the internalization of vesicles and the role of the therapeutic molecules (identified by mirn-, transcript-, prote-, lipid-ome). The preclinical study will consist in grafting OSC-EV into a venous bridge, inserted between the 2 ends of a rat peroneal nerve defect of 1 cm (20 million EV/10 µL). As a control condition, an EV-free culture medium will be inserted in the conduit with biological glue. Two modes of delivery will be tested: 1) grafting at the time of surgery and 2) grafting at the time of surgery and into a micro-pump that will diffuse the OSC-EV (throughout per week during 1 month). The motricity, the sensitivity, the electrophysiological properties, the axogenesis and the myelinization will be evaluated.

Expected results

Our team showed the OSC-EV efficacy in the differentiation of neuron progenitors with an increase in the number and length of neurites in an in-vitro assay. We expect to understand the cellular and the molecular processes underlying the nerve regeneration, to identify the therapeutic EV molecules, to prove the low immunogenicity of the EV and develop a cell-free strategy that could be transferable to humans.

Feasibility

NOSE team is known for its expertise in OSC biology. This project will benefit from a full access to cell culture rooms, an animal facility, a cutting-edge microscopy platform, molecular biology tools, in vivo platforms. All techniques and tools required by this project are routinely used in the laboratory and are mastered by the teams.

Expected candidate profil

Strong research interest in PNS injuries, expertise in surgical techniques/microsurgery, comfortable with animal experiment, basic knowledge of stem cells and EV

SUPERVISED PHDS & PUBLICATIONS : GUIRAUDIE-CAPRAZ Gaelle

- **Previously supervised PhD students**

- Fanny Gaudel, 2015-2018

- **Publications of previously supervised PHD students (last 5 years)**

- **Gaudel F**, Féron F & **Guiraudie-Capraz G** (2021) Limbic expression of mRNA coding for chemoreceptors in human brain – Lessons from brain atlases. Int. J. Mol. Sci. 22(13), 6858. doi.org/10.3390/ijms22136858
- **Gaudel F**, Stephan D, Landel V, Sicard G, Féron F & **Guiraudie-Capraz G** (2019) Expression of the cerebral olfactory receptors Olfr110/111 and Olfr544 is altered during aging and in Alzheimer's disease-like mice. Molecular Neurobiology. DOI: 10.1007/s12035-018-1196-4

PROJECT MD2

Title : MOSAIC therapy in the treatment of posttraumatic stress disorder: a study of non-inferiority to EMDR and superiority to a control group

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Project summary

Post-traumatic stress disorder (PTSD) is a highly prevalent (8-10%) and difficult-to-treat disorder induced by exposure to threat of serious injury or death to oneself or others. PTSD treatment guidelines recommend trauma-focused therapies as first-line treatments, including eye movement desensitization and reprocessing (EMDR), one of the most currently delivered therapy. Despite the proven efficacy of EMDR, 30% of patients fail to complete the therapy due to trauma re-exposure during sessions (Hembree, 2003). Non-trauma-focused therapies have been therefore developed to improve the acceptability with decreased dropout and increased well-being during sessions. However, they are less efficient than trauma-focused therapies and their effectiveness should be improved (Bisson et al., 2013). Mouvements Oculaires et Stimulations Alternées pour l'Intégration Cérébrale (MOSAIC) has been therefore developed to improve the effectiveness of non-trauma focused therapies for PTSD. MOSAIC uses the efficiency of EMDR's eye movements but instead of reliving the trauma memory to desensitize the negative emotions, it allows patients to live in their body what they want to feel (peacefulness, joy ...). Pilot data from a hospital open trial comparing 10 PTSD patients receiving MOSAIC and 10 EMDR report similar PTSD symptoms decrease in both groups (PCL-5 scores: 42.0 ± 4.4 vs. 33.3 ± 5.9 respectively) ($t=1.1$, $p> 0.05$). As expected, the dropout rate tends to be much lower in MOSAIC than EDMR (9 % vs. 22%, $p> 0.05$). In contrast, well-being scores during and between the therapy sessions are significantly higher in the MOSAIC than in the EMDR group ($p<0.05$). This study was conducted following a standardized MOSAIC protocol published as an article in the American Journal of Psychotherapy (Khalfa & Poupard, 2020) and in a book (Khalfa, 2021). The objectves of this research is to verify that 1) MOSAIC therapy is as effective as EMDR therapy in alleviating PTSD symptoms, anxiety and depression at 3- and 6-months posttreatment 2) MOSAIC has a better acceptability than EMDR (higher well-being, less dropout) 3) MOSAIC is more effective than a supportive therapy. The research is a single-blind, three-arm, non-inferiority and randomized controlled trial comparing MOSAIC, EMDR and supportive therapies in PTSD, using validated questionnaires for assessing PTSD symptoms, anxiety, depression, and well-being. We expect verifying our three objectives. A collaboration already in place with hospital specialized in psychotrauma (La Conception in Marseille and Montfavet in Avignon) will allow for the recruitment and treatment of PTSD patients thus ensuring the feasibility of the study. Expected skills for the candidate are experience with psychotrauma, experience in psychiatry, good level to read English, background knowledge in statistics

SUPERVISED PHDS & PUBLICATIONS : KHALFA Stéphanie

- **Currently supervised PhD students**

- Déborah Flatot-Blin

- **Previously supervised PhD students**

- El-Khoury Myriam (2008-2011)
- Reynaud Emmanuelle (2009-2012)
- Boukkezzi Sarah (2013-2017)

- Rousseau Pierre-François (2013-2018)

- **Publications of previously supervised PHD students (last 5 years)**

- Boukezzi S, Baunez C, Rousseau P-F, Warrot D, Silva C, Guyon V, Zendjidjian X, Nicolas F, Guedj E, Nazarian B, Trousselard M, Chaminade T, Khalfa S. Posttraumatic Stress Disorder is associated with altered reward mechanisms during the anticipation and the outcome of monetary incentive cues. Neuroimage: Clinical. 2019; 25: 102073
- Rousseau PF, Malbos E, Verger A, Nicolas F, Lançon C, Khalfa S, Guedj E. Increase of precuneus metabolism correlates with reduction of PTSD symptoms after EMDR therapy in military veterans: an 18F-FDG PET study during virtual reality exposure to war. European Journal of Nuclear Medicine and Molecular Imaging. 2019; 46(9): 1817-1821
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- Rousseau PF, El Khoury-Malhame M, Reynaud E, Zendjidjian X, Samuelian JC, Khalfa S. Neurobiological correlates of EMDR therapy effect in PTSD. European Journal of Trauma and Dissociation. 2018; 3(2): 103-111
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- El-Khoury-Malhame M., Reynaud E., Beetz E-M., Khalfa S (2017) Restoration of Emotional control ability in PTSD Following Symptom Amelioration by EMDR therapy. European Journal of Trauma and Dissociation. 1(1): 73-79
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