Université de Paris

master BMC
Biologie Moléculaire et Cellulaire

Proposition de Stage de M2

Conventions : Sorbonne Université, Université Sorbonne Paris Nord, Université Paris Saclay, Muséum National d'Histoire Naturelle, Institut Pasteur

Année Universitaire 2020-2021

Equipe d'Accueil : NeuroDiderot

Intitulé de l'Unité : INSERM UMR1141- *NeuroDiderot* -Université de Paris, Hôpital Robert Debré,

Nom du Responsable de l'Unité : P. Gresse

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9 Parcours de M2

(plusieurs parcours peuvent être choisis)

- Biologie moléculaire, cellulaire et fonctionnelle de l'hématopoïèse ☐
Responsables: S. Giraudier, N. Dulphy, E. Lauret

- Biomolécules, biologie et pathologie moléculaires X☐
Responsables: JM. Dupret, F. Rodrigues-Lima

- Biologie et développment cellulaires X☐
Responsables: A. Guichet, A. Benmerah

- Inflammation et maladies inflammatoires ☐
Responsables: R. Monteiro, L. Mouthon, D. Ledoux

- Biothérapeutiques: Conception et applications ☐
Responsables: I. Garcia-Verdugo, JM. Sallenave

- Immunologie et Immunopathologies ☐
Responsables: M. Viguier, E. Tartour

- Microbiologie ☐
Responsables: I. Martin-Verstraete, X. Nassif

- Virologie ☐
Responsables: S. van der Werf, F. Rozenberg

- Microbiologie et génie biologique ☐

Responsables: O. Dussurget

Titre du sujet de recherche : Effect of Seizures on the Developing Brain and Cognition

Résumé du projet (environ une demi-page)

Epilepsy is the most frequent neurological disorder, affecting approximately 1% of people worldwide. The disease is characterized by recurrent seizures due to synchronous hyperexcitation of large populations of brain neurons. Moreover, in severe developmental and epileptic encephalopathies caused by early brain defects, such as Dravet syndrome, violent and frequent seizures during the very first years of life frequently cause permanent psychomotor deficits and recurrent seizures. Numerous antiepileptic drugs have been developed, but they are ineffective in at least one-third of patients, especially for developmental and epileptic encephalopathies children, a failure likely related to the neurocentrism of these therapies, which have so far almost completely overlooked non-neuronal cells, and especially microglia, the resident brain macrophages. It has long been known that seizures induce MG-mediated brain inflammation and massive secretion of pro-inflammatory mediators,a complex and highly regulated process that is mainly mediated by microglia, a population of resident macrophages, which colonize the cerebral parenchyma during early brain development in vertebrates. However, while neuroinflammation was seen until recently as a mere consequence of neuron over-excitation, recent data suggest that microglial cell activities play an important role in the physiopathology of epilepsy. However, and most importantly, whether microglia activities are beneficial or, on the contrary, harmful for post-seizure brain functioning, is an unresolved and critical issue that has tremendous implications for the development of novel therapeutic strategies

The goal of this project thesis is to better understand the role of microglial cells in epilepsy. For this, our team takes advantage of the large set of *in vivo* approaches allowed by the zebrafish (*Danio rerio*). Specifically, we combine genetic techniques (epileptic mutant lines and transient gene knock-down) with imaging (confocal microscopy and calcium imaging), electrophysiological (EEG) and molecular approaches, to precisely characterize the phenotypic and molecular changes of microglial cells, which are induced by epileptic seizures, and better understand the consequences of these changes on subsequent brain functioning and neuron excitation.

Publications les plus significatives dans la période de référence (2017-2021)

1. Brenet A, Hassan-Abdi R, and **Soussi-Yanicostas N.**
Bixafen, a succinate dehydrogenase inhibitor fungicide, causes microcephaly and motor neuron axon defects during development.
Chemosphere. 2020 Oct 27:128781. doi: 10.1016/j.chemosphere.2020.128781

2. Brenet A, Somkhit J, Hassan-Abdi R, Yanicostas C, Romain C, Bar O, Igert A, Saurat D, Taudon N, Dal-Bo G, Nachon F, Dupuis N, and **Soussi-Yanicostas N.**
Organophosphorus diisopropylfluorophosphate (DFP) intoxication in zebrafish larvae causes behavioral defects, neuronal hyperexcitation and neuronal death
Sci Rep. 2020 Nov 5;10(1):19228. doi: 10.1038/s41598-020-76056-8.

3. Maupu C, Enderlin J, Igert A, Oger M, Auvin S, Hassan-Abdi R, **Soussi-Yanicostas N,** Brazzolotto X, Nachon F, Dal Bo G, Dupuis N.Diisopropylfluorophosphate-induced status epilepticus drives complex glial cell phenotypes in adult male mice.
***Neurobiol Dis*. 2021** Jan 30;152:105276.

4. Brenet A, Hassan-Abdi R, Somkhit J, Yanicostas C, and **Soussi-Yanicostas N**
Defective Excitatory/Inhibitory Synaptic Balance and Increased Neuron Apoptosis in a Zebrafish Model of Dravet Syndrome
Cells. 2019 Oct 4;8(10). pii: E1199. doi: 10.3390/cells8101199.

5. Mairesse J, Zinni M, Pansiot J, Hassan-Abdi R, Demene C, Colella M, Charriaut-Marlangue C, Rideau Batista Novais A, Tanter M, Maccari S, Gressens P, Vaiman D, Baud* O, and **N Soussi-Yanicostas***
Co-last authors.
Oxytocin receptor agonist reduces perinatal brain damage by targeting microglia.
Glia. 2019 Feb;67(2):345-359. doi: 10.1002/glia.23546.

6. Van Steenwinckel J, Schang A-L, Krishnan ML, et al. **N Soussi-Yanicostas** , B Fleiss , P Gressens.
Decreased microglial Wnt/β-catenin signalling drives microglial pro-inflammatory activation in the developing brain.
***Brain*. 2019**;142(12):3806-3833. doi:10.1093/brain/awz319

7. Alavi Naini SM, Yanicostas C, Hassan-Abdi R, Blondeel S, Bennis M, Weiss RJ, Tor Y, Esko JD, and **Soussi-Yanicostas N.**
Surfen and oxalyl surfen decrease tau hyperphosphorylation and mitigate neuron deficits in vivo in a zebrafish model of tauopathy.
Transl Neurodegener. 2018 Mar 16;7:6. doi: 10.1186/s40035-018-0111-2.

8. Naini SMA, **Soussi-Yanicostas N.**
Heparan sulfate as a therapeutic target in tauopathies: Insights from zebrafish.
Front Cell Dev Biol. 2018;6(DEC). doi:10.3389/fcell.2018.00163

9. Samarut É, Swaminathan A, Riché R, Liao M, Hassan-Abdi R, Renault S, Allard M, Dufour L, Cossette P, **Soussi-Yanicostas N**, Drapeau P.

γ-Aminobutyric acid receptor alpha 1 subunit loss of function causes genetic generalized epilepsy by impairing inhibitory network neurodevelopment.
Epilepsia. 2018;(September):2061-2074. doi:10.1111/epi.14576.

10. Auvin S, Jeljeli M, Desnous B, **Soussi-Yanicostas N**, Dournaud P, Sterkers G.
Altered vaccine-induced immunity in children with Dravet syndrome.
Epilepsia. 2018;59(4):e45-e50. doi:10.1111/epi.14038

11. Swaminathan A, Hassan-Abdi R, Renault S, Siekierska A, Riché R, Liao M, de Witte PAM, Yanicostas C, **Soussi-Yanicostas N**, Drapeau P,and Samarut É.
Non-canonical mTOR-Independent Role of DEPDC5 in Regulating GABAergic Network Development.
Curr Biol. 2018 Jun 18;28(12):1924-1937. doi: 10.1016/j.cub.2018.04.061.

12. Alavi Naini SM, Yanicostas C, Hassan-Abdi R, Blondeel S, Bennis M, Weiss RJ, Tor Y, Esko JD, and **Soussi-Yanicostas N.**
Surfen and oxalyl surfen decrease tau hyperphosphorylation and mitigate neuron deficits in vivo in a zebrafish model of tauopathy.
Transl Neurodegener. 2018 Mar 16;7:6. doi: 10.1186/s40035-018-0111-2.

13. Somkhi J, Loyant R, Brenet A, Hassan-Abdi R, Yanicostas Y, Porcedd M, Borgne-Sanchez A, and **Soussi-Yanicostas N**.
A fast, simple and affordable technique to measure oxygen consumption rates in living zebrafish embryos.
Zebrafish, 2020, doi: 10.1089/zeb.2020.1878

14. Hassan-Abdi R, Brenet A, Bennis M, Yanicostas C, and **Soussi-Yanicostas N**
Neurons Expressing Pathological Tau Protein Trigger Dramatic Changes in Microglial Morphology and Dynamics
Front Neurosci. 2019 Nov 7;13:1199. doi: 10.3389/fnins.2019.01199.

Patents

- **Soussi-Yanicostas N,** Yanicostas C, Alavi-Naini MS. 2011. Materials and methods for the treatment of tauopathies. International patent (deposit number: PCT/EP2012106523, Inserm Transfert).
- Papy-Garcia D, Huyn B, **Soussi-Yanicostas N,** et al. 2012. European patent (deposit number: 12300005414.0-2107). Method of diagnosis, pronostic or treatment of neurodegenerative diseases. This patent was extended to USA (deposit 01/06/2016, Deposit number 15/196,180), deposit: SATT Ile-de-France Innov.

Ce projet s'inscrit-il dans la perspective d'une thèse :

oui X☐
non ☐

si oui type de financement prévu :

Ecole Doctorale de rattachement : Ecole doctorale BioSPC

Fiche à retourner par e-mail au secrétariat du Master (UFR des Sciences du Vivant, Université de Paris), M. Aristide HENAULT (aristide.henault@u-paris.fr)