Ph.D. program icn integrative & clinical neuroscience

Aix-Marseille University (AMU)

PhD program in Integrative and Clinical Neuroscience

PhD Scholarships

2018 Call for Research Projects

Maximum one research project per team

Laboratory: Developmental Biology Institute of Marseille (IBDM)

Head of the laboratory: André Le Bivic

Team name:

Team leader(s): Laurent Fasano

First name and last name of the proposed PhD supervisor(s): Xavier Caubit

Title of the proposed PhD research project:

From novel *Tshz3* mouse models to understanding pathophysiology of autism spectrum disorder

Names and PhD year of the currently supervised PhD students:

Irene Sanchez-Martin, 3rd year

Names and dates of the previously supervised PhD students:

1. M. Armel Gallet - Thèse soutenue en 1999
2. Mlle Corinne Angelats - Thèse soutenue en 2000
3. Mme Ouarda Taghli-Lamalem - Thèse soutenue en 2001.
4. M. Daniel Papillon - Thèse soutenue en 2004
5. M. Hervé Faralli - Thèse soutenue en 2010.
6. Mlle Elise Martin - Thèse soutenue en 2010
7. Mlle Silvia Pimentel - Thèse soutenue en 2011 (Lisbonne ; Portugal).

Publications of the previously supervised PhD students (underline the names):

1. Martin E, Caubit X, Airik R, Vola C, Fatmi A, Kispert A, Fasano L. TSHZ3 and SOX9 Regulate the Timing of Smooth Muscle Cell Differentiation in the Ureter by Reducing Myocardin Activity. **PLoS One**. 2013 May 6;8(5)
2. "Teashirt in cell proliferation "; Silvia Pimentel, Rui Gomes and Laurent Fasano; LAP Lambert Academic Publishing (2012). ISBN 978-3-8484-2850-2.

3. Faralli H, Martin E, Coré N, Liu QC, Filippi P, Dilworth FJ, Caubit X, Fasano L. Teashirt-3, a novel regulator of muscle differentiation, associates with BRG1-associated factor 57 (BAF57) to inhibit myogenin gene expression. J Biol Chem. 2011 Jul 1;286(26):23498-510.
4. Caubit X, Thoby-Brisson M, Voituron N, Filippi P, Bévengut M, Faralli H, Zanella S, Fortin G, Hilaire G, Fasano L. *Teashirt3* regulates development of neurons involved in both respiratory rhythm and airflow control. **J Neurosci.** 2010 Jul 14;30(28):9465-76.
5. Caubit X[1], Lye CM[1], Martin E[1], Coré N, Long DA, Vola C, Jenkins D, Garratt AN, Skaer H, Woolf AS, Fasano L. Teashirt 3 is necessary for ureteral smooth muscle differentiation downstream of SHH and BMP4. **Development**. 2008 Oct;135(19):3301-10. [1] first co-authors.
6. Taghli-Lamallem O, Gallet A, Leroy F, Malapert P, Vola C, Kerridge S, Fasano L. Direct interaction between Teashirt and Sex combs reduced proteins, via Tsh's acidic domain, is essential for specifying the identity of the prothorax in Drosophila. **Dev Biol**. 2007 Jul 1;307(1):142-51.
7. Marlétaz F, Martin E, Perez Y, Papillon D, Caubit X, Lowe CJ, Freeman B, Fasano L, Dossat C, Wincker P, Weissenbach J, Le Parco Y. Chaetognath phylogenomics: a protostome with deuterostome-like development. **Curr Biol**. 2006 Aug 8;16(15):R577-8.
8. Papillon D, Perez Y, Caubit X, Le Parco Y. (2006). Systematics of Chaetognatha under the light of molecular data, using duplicated ribosomal 18S DNA sequences. **J. Mol. Phyl. Evol**. 38(3):621-34.
9. Papillon D, Perez Y, Fasano L, Le Parco Y, Caubit X. Restricted expression of a median Hox gene in the central nervous system of chaetognaths. **Dev Genes Evol**. 2005 Mar 24
10. Papillon D, Perez Y, Caubit X, Le Parco Y. (2004)**.** Identification of Chaetognaths as Protostomes Is Supported by the Analysis of Their Mitochondrial Genome. **Mol Biol Evol**. 21(11):2122-29.
11. Papillon D, Perez Y, Fasano L, Le Parco Y, Caubit X. Hox gene survey in the chaetognath Spadella cephaloptera: evolutionary implications. **Dev Genes Evol**. 2003 Apr;213(3):142-8. Epub 2003 Mar 11.
12. Nicolas S, Papillon D, Perez Y, Caubit X, Le Parco Y (2003). The spatial restrictions of 5'HoxC genes expression are maintained in adult newt spinal cord. **Biol Cell.** 95(9):589-94.
13. Angelats C, Gallet A, Therond P, Fasano L, Kerridge S. Cubitus interruptus acts to specify naked cuticle in the trunk of Drosophila embryos. **Dev Biol**. 2002 Jan 1;241(1):132-44.
14. Erkner A, Roure A, Charroux B, Delaage M, Holway N, Core N, Vola C, Angelats C, Pages F, Fasano L, Kerridge S. Grunge, related to human Atrophin-like proteins, has multiple functions in Drosophila development. **Development**. 2002 Mar;129(5):1119-29.
15. Gallet, A, Erkner A, Charroux B, Fasano L, Kerridge S (1999). The C-terminal domain of Armadillo binds to hypophosporylated Teashirt to modulate Wingless signalling in Drosophila. **EMBO. J**. Apr 15;18(8):2208-17.
16. Erkner A, Gallet A, Angelats C, Fasano L, Kerridge S (1999). The Role of Teashirt in Proximal Leg Development in Drosophila: Ectopic teashirt Expression

Reveals Different Cell Behaviours in Ventral and Dorsal Domains. **Dev Biol** Nov 15;215(2):221-232

17. Gallet A, Erkner A, Charroux B, Fasano L, Kerridge S (1998). Trunk-specific modulation of wingless signalling in Drosophila by teashirt binding to armadillo. **Curr Biol**. 1998 Jul 30-Aug 13;8(16):893-902.
18. E. Alexandre, Y. Graba, L. Fasano, A. Gallet, L. Perrin, P. de Zulueta, J. Pradel, S. Kerridge and B. Jacq. (1996). The *Drosophila* Teashirt homeotic protein is a DNA-binding protein and *modulo*, a HOM-C regulated modifier of variegation, is a likely candidate for being a direct targets gene. **Mechanisms of Development** 59, 191-204.

Summary of the proposed research project (Max. 1 page)

- **State of the art**

Recently, we identified *TSHZ3* as a critical gene defining a new syndrome including autistic features in patients with 19q12 deletion and provided evidence, from studies in mouse models, for a link between *Tshz3* deletion, defects in cortical projection neurons and autism spectrum disorder (ASD)-like deficits (Caubit et al., Nature Genet. 2016. PMID 27668656).

- **Objectives**

The main aim of the project will be to study **when, where and how** TSHZ3 function is critical for the proper development and function of the brain.

- **Methods**

The successful PhD candidate will address this question by combining **molecular, morphological, behavioral** and **electrophysiological** approaches to characterize a new mouse model with conditional removal of *Tshz3* in cortical projection neurons (CPNs; ***Where***) from post-natal day (P) 2-3 onward (***When***). To address the **how**, the candidate will use large-scale screening (RNA-seq) to identify differentially expressed genes in the cerebral cortex of wild-type *vs.* mutant mice. To identify direct targets of TSHZ3 he/she will perform *in vivo* chromatin immunoprecipitation (ChIP) experiments. The enriched DNA will be sequenced (ChIP-seq) and the TSHZ3 target sites will be identified using bioinformatics analysis.

- **Expected results**

This project will allow 1) determining the contribution of embryonic *vs.* post-natal processes to the ASD-related behavioral deficits and alterations in CPNs function associated with *Tshz3* deficiency and 2) identifying for the first time, the direct targets of TSHZ3. Based on our preliminary results (see “Feasibility”) completion of the project will pave the way to determine whether genetically restoring *Tshz3* expression after birth in specific neuronal populations improves ASD-like deficits of *Tshz3* heterozygous mice and identify novel potential molecular targets for therapeutic approaches.

- **Feasibility over the 3-year period, including project financial support and ethics committee authorizations**

We have confirmed that Cre activity inactivates *Tshz3* in CPNs. Our preliminary data suggest that **postnatal deletion of *Tshz3* is sufficient to generate social interaction deficit**. We have strong internal collaboration with Lydia Kerkerian Le Goff Team (electrophysiology) and Bianca Habermann Team (Bioinformatics).

- **Expected candidate profile**

For this neuroscience PhD project, we seek one motivated pre-graduate candidate. Training will be provided in molecular biology, developmental biology, mouse genetics and behavioural testing. Prior experience with mouse genetics is beneficial but not mandatory. Good knowledge of English will be appreciated but any good application will be considered. This project has the support of the ANR ("TSHZ3inASD", 2018-2020)