

## INTERNSHIP PROPOSAL

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**Research project title:** Targeted mutagenesis of the deubiquitinating enzyme USP8 using the CRISPR-Cas9 technology

**5 Keywords to describe the project:** endocytosis, RTK signalling, ubiquitin, CRISPR-Cas9, *Drosophila*

### **Description of the project (aims, experimental techniques, recommended background):**

Ubiquitination is a post-translational modification which regulates many cellular processes and, by removing ubiquitin from ubiquitinated substrates, deubiquitinating enzymes (DUBs) are key players in these processes. The DUB USP8 plays a major role in endocytosis and thereby regulates many signaling pathways involving receptor tyrosine kinases (RTKs). In *Drosophila*, it regulates the intracellular signaling of the Hedgehog and Frizzled pathways. In human, USP8 regulates the epidermal growth factor receptor (EGFR) pathway which is involved in many oncogenic processes. Moreover, mutations in the USP8 gene are frequently associated with Cushing's pituitary tumors. It is thus crucial to have a better understanding of USP8 functions. To this end, we propose to generate new mutations of the Usp8 gene in *Drosophila* using the CRISPR-Cas9 technology. This technology has already been successfully used in our team and will allow us to generate inactivating as well as hyper-activating mutations of USP8. In the long run, our goal is to establish a *Drosophila* model of the Cushing's disease. The applicant should have a Master degree in biology and strong interests in molecular biology, genetics and cell biology.

### **Relevant publications of the team:**

1. Jacomin, A. C., Fauvarque, M. O., and Taillebourg, E. (2016) A functional endosomal pathway is necessary for lysosome biogenesis in *Drosophila*, *BMC Cell Biology*, 17(1) :36.
2. Jacomin, A. C., Bescond, A., Soleilhac, E., Gallet, B., Schoehn, G., Fauvarque, M. O., and Taillebourg, E. (2015) The Deubiquitinating Enzyme UBPY Is Required for Lysosomal Biogenesis and Productive Autophagy in *Drosophila*, *PLoS one* 10, e0143078.
3. Engel, E., Viargues, P., Mortier, M., Taillebourg, E., Coute, Y., Thevenon, D., and Fauvarque, M. O. (2014) Identifying USPs regulating immune signals in *Drosophila*: USP2 deubiquitinates Imd and promotes its degradation by interacting with the proteasome, *Cell communication and signaling : CCS* 12, 41.