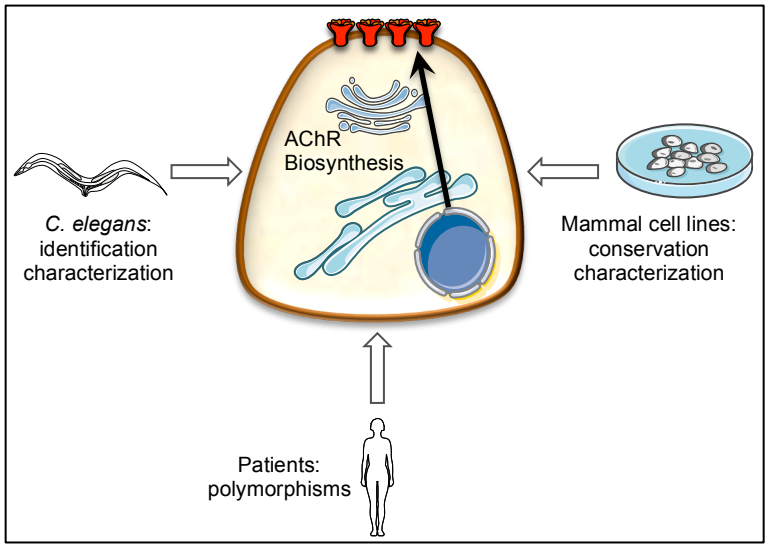
Genetic control of acetylcholine receptor biosynthesis: from *C. elegans* to human pathologies.

Keywords: synapse, AChRs, translational research, neuromuscular junction



Acetylcholine ionotropic receptors (AChR) are supporting the neurotransmission at the neuromuscular junction and have a neuromodulator action in the central nervous system. Dysfunction of these receptors, such as a decrease of the receptor numbers, is linked to several pathologies, including myasthenia, schizophrenia or epilepsy. The **quantity of the receptors at the plasma membrane is thus finely tuned** and results from a balance between biosynthesis, recycling or degradation of the receptors.

One axis of our research aims to **identify and characterize new factors involved in the biosynthesis of the AChR**.

Our strategy consists in:

1. identifying new factors involved in AChR biosynthesis using the model organism ***Caenorhabditis elegans***,
2. characterizing the function of these factors in *C. elegans*,
3. testing the **conservation** of the function in a **human neuronal cell line**,
4. checking in the database of **rare diseases** if **polymorphisms** on the identified genes have been associated with human pathologies and, if applicable, introducing the same polymorphism in *C. elegans* genome to test the potential pathogenicity of the mutation.

During the internship, the student will characterize two proteins, **TMED7 and TMED2**, which have been identified by a genetic screen conducted in *C. elegans*. TMED7 and TMED2 are involved in endoplasmic reticulum to Golgi vesicle-mediated transport. Until now, they have never been linked to AChR biosynthesis. Our preliminary data show that the quantity of the AChRs at the neuromuscular junction of *C. elegans* is reduced of more than 50% in mutants for TMED7 or TMED2.

More specifically the student will:

- confirm the preliminary data by imaging the receptors endogenously tagged with t-RFP in TMED mutants with a **confocal spinning disk system**,
- determine the subcellular localization of TMED7 and TMED2 by editing *C. elegans* genome using the **CRISPR/Cas9 technology** to insert a fluorescent tag into the loci encoding the proteins,
- build by **genetic crosses** the double mutant TMED7/TMED2 and characterize the phenotype of the worms by **behavioral tests**,
- measure the impact of TMED absence on muscle function using **calcium imaging** experiments.

The student will be working with a post-doctoral researcher and under the supervision of a permanent researcher. Only candidates with high-quality academic results will be interviewed. We ask the candidates to send a cv and a one-page motivation letter (in French or in English; the letter has to expose the interests of the candidate into the project) to maelle.jospin@univ-lyon1.fr.

Related publications:

D'Alessandro M, **Richard M**, Stigloher C, Gache V, Boulin T, Richmond JE, **Bessereau JL** (2018) CRELD1 is an evolutionarily-conserved maturational enhancer of ionotropic acetylcholine receptors. Elife 7 pii: e39649.

Abiusi E, **D'Alessandro M**, Dieterich K, Quevarec L, Turczynski S, Valfort AC, Mezin P, Jouk PS, Gut M, Gut I, **Bessereau JL**, Melki J (2017) Biallelic mutation of UNC50, encoding a protein involved in AChR trafficking, is responsible for arthrogryposis. Hum Mol Genet 26:3989-3994.