

**Master 2 internship project
Year 2024-2025**

Laboratory/Institute: Grenoble Institut Neurosciences (GIN) **Director:** Dr. E. Barbier

Team: Intracellular Dynamics and Neurodegeneration

Head of the team: F. Saudou, PUPH

Name and status of the scientist in charge of the project: Fabienne Agasse, MCU

HDR: yes no

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Program of the Master's degree in Biology:

- Microbiology, Infectious Diseases and Immunology Structural Biology of Pathogens
 Physiology, Epigenetics, Differentiation, Cancer Neurosciences and Neurobiology

Title of the project: Neural stem cells in Huntington disease and aging

Objectives (up to 3 lines):

In a mouse model of Huntington disease (HD), the candidate will: i) evaluate the maintenance of stem cells in the testis, skin and intestine; ii) determine whether proliferation and neural differentiation are affected and iii) whether metformin can restore these effects.

Abstract (up to 10 lines):

Neurogenesis, the process by which new neurons are added from a resident pool of stem cells, is decreased in Huntington disease (HD). HD is a genetic neurological disorder with autosomal dominant transmission of the mutated huntingtin (*HTT*) gene. Onset of the disease occurs around 40 years old and is characterized by a triad of motor, cognitive and psychiatric symptoms. The HD mutation consists of an abnormal expansion of a CAG repeat, exceeding 35, in the *HTT* gene coding for a polymorphic polyglutamine (polyQ) stretch. Mutant *HTT* (mHTT) is toxic for neurons. In HD, neurogenesis is decreased in the dentate gyrus of the hippocampus in humans but also in the subventricular zone of rodents, impairing odor discrimination and memory. Our previous data showed that mHTT accelerates aging, depleting the stem cell pool which impairs neurogenesis. As mHTT is widely expressed throughout the organism, we speculate that other stem cell pools are affected. Also, we hypothesize that treating HD mice with a senomorphic may restore neurogenesis.

Methods (up to 3 lines):

Western blot, cell culture, immunocytochemistry, histochemistry, flow cytometry, microscopy.

Up to 3 relevant publications of the team:

Barnat M, Capizzi M, Aparicio E, Boluda S, Wennagel D, Kacher R, Kassem R, Lenoir S, Agasse F, Braz BY, Liu JP, Ighil J, Tessier A, Zeitlin SO, Duyckaerts C, Dommergues M, Durr A, Humbert S (2020). Huntington's disease alters human neurodevelopment. *Science*, 369(6505):787-793.

Agasse F, Mendez-David I, Christaller W, Carpentier R, Braz BY, David DJ, Saudou F, Humbert S. (2020) Chronic Corticosterone Elevation Suppresses Adult Hippocampal Neurogenesis by Hyperphosphorylating Huntingtin. *Cell Rep.*, 32(1):107865.

Requested domains of expertise (up to 5 keywords):

Neuroscience, Cellular biology.