Molecular adaptations, nuclear organization in enduring social aversion, a preclinical model of depression.

Stress response participates to life-long behavioral adaptations to environmental changes (Barik *et al.* 2023, Battivelli *et al.* 2024). Those may be beneficial, for instance in adjusting social interactions to congeners, but may also lead to the appearance of behavioral disorders. Enduring behavioral changes are underpinned by long-lasting neuroadaptation, thought to arise from changes in gene expression stabilized via epigenetic mechanisms. We showed that the glucocorticoid receptor (GR) and its partner SWI/SNF remodeler complex are required in the nucleus accumbens (NAc) for the appearance of social aversion following repeated social defeats (RSD), a reasonable adaptation and a model of depression (Barik *et al.* 2013, Zayed *et al.* 2022). When exposed to RSD, around 60 % of individual mice are susceptible and develop aversion whereas the other ones are resilient. Inactivation in the NAc of Brg1 gene, encoding for the SWI/SNF catalytic subunit, of GR gene shift all individuals to resiliency. The project we will further dig the molecular mechanisms in play and the behavioral consequences.

Altogether, these results posit the BAF complexes and gene *Brg1* as keys within the NAc in adaptive transcriptional responses to stress and ensuing behavioral changes. The first aim of the PhD thesis is to uncover the molecular changes associated with gene expression neuronal plasticity and responsible for underlying persistent behavioral adaptations following repeated social defeats. The second is to understand whether the induction of social avoidance can be pharmacologically blocked and/or reverted a posteriori, thus paving the way for novel therapeutic targets for stress-related diseases.

Work plan.

First task, we will set-up study the neuronal population activated in the NAc by a social defeat. We will address this question using viral-TRAP approach that enables inducible activity-dependent long-term tagging of FOS expressing neurons (Matos *et al.* 2029). We will investigate whether the same neuronal population is activated by repeated social defeats, will study the dynamics of neuronal recruitment and will address the role of GR and BRG1 in their activation.

Second task, will investigate nuclear plasticity by following RSD by SHAREseq approach that combines ATACseq and RNAseq in NAc single nuclei (Ma *et al.* 2020). We will therefore assess the dynamics of genome expression and nuclear organization through chromatin compaction. We will perform this study at different time points in C57BL/6 males exposed to a unique social defeat, that do not induce social aversion, and mice exposed to ten repeated social defeats that do. We will distinguish between resilient and susceptible mice. This should allow us to tackle enduring molecular changes, in different NAc cell populations that sustain long term behavioral changes in susceptible mice.

Third task, in this framework, we will assess the hypothesis that a pharmacological intervention with the ketone body β-hydroxybutyrate (BHB) is able to promote stress resilience. This hypothesis is substantiated on one hand by the current knowledge on candidate stress resilience mechanisms and, on the other hand, on data showing that ketogenic signaling improves behavioral deficits and is able to positively modulate many of the potential resilience mechanisms (Yamanashi *et al*. 2020). BHB is produced by the body following fasting, physical exercise and ketogenic diet. We will study whether BHB can prevent or cure RSD induced social aversion and other behavioral consequences of RSD. At the molecular level, the beneficial effects of BHB most probably implicates epigenetic mechanisms. BHB can indeed be covalently linked to H3K9 and H3K14, a new type epigenetic mark associated with caloric restriction or a ketogenic diet. Interestingly, it might interfere with SWI/SNF chromatin remodeler complexes recruitment on chromatin since acetylation of H3K9 and H3K14 facilitates SWI/SNF docking on chromatin. We will address this question combining, epigenomics (SHAREseq, ChIPseq) and mutant mouse models. If BHB treatment is not efficient, we will test other potential

therapeutic treatments targeting GR or BRG1. Two compounds are of particular interest. The BRG1 inhibitor called PFI-3 is commercially available and passes the brain-blood barrier (Yang *et al.* 2021), and the GR Cort113176 antagonist targeting more specifically the interaction between GR-and BRG1-containing remodeler complexes (Gentenaar *et al.* 2024).

The expected results will contribute to substantiate the role of nuclear plasticity and to identify molecular mechanisms underlying stress-related behavioral changes. A better fundamental understanding of these processes is essential to make possible the evolution of therapeutic solutions for neuropsychiatric diseases related to stress.

A large part of the PhD project takes place within an ERA-Net Neuron project entitled « Ketogenic signaling in resilience promotion » (Ketoresi) that started in November 2024 and involves teams from Germany (B. Lutz and A Sebastian, Mainz), Spain (M Claret, Barcelona), Italy (M Morena) and France (F Tronche) with whom we will collaborate. Beat Lutz (University of Mainz) will be cosupervisor of the PhD. The Ketoresi project addresses molecular and cellular adaptations induced in the NAc and responsible for susceptibility or resilience to social defeat, with focus on the role of GR and Brg1 in this process and the effects of a BHB treatment. It addresses this question in both preclinical models and in humans.
For the scientific mediation part, the PhD student will be enrolled in the organization of the “Brain Awareness Week” (Semaine du Cerveau) of which François Tronche is national coordinator. This event takes place every year in March. In 2024, there was around 700 events in France (conferences, debates, science cafés, theater plays, exhibitions, etc., in all regions of France (134 cities). The student will participate in the programmation, contacts with media, organization of the “opening conference”. She/he will also yearly participate to debates of conferences in Paris or in Limousin where she/he will have the opportunity to present or discuss his/her own research projects.

References (host team ones are indicated in blue)

Barik J, Marti F, Morel C, Fernandez SP, Lanteri C, Godeheu G, Tassin JP, Mombereau C, Faure P, Tronche F. ***Science***. 2013; 339(6117): 332-5. link

Battivelli D, Vernochet C, Conabady E, Nguyen C, Zayed A, Lebel A, Meirsman AC, Messaoudene S, Fieggen A, Dreux G, Rigoni D, Le Borgne T, Marti F, Contesse T, Barik J, Tassin JP, Faure P, Parnaudeau S, Tronche F. Dopamine Neuron Activity and Stress Signaling as Links Between Social Hierarchy and Psychopathology Vulnerability. ***Biological Psychiatry***. 2024. 95(8):774-84. link

Gentenaar M, Meulmeester FL, van der Burg XR, Hoekstra AT, Hunt H, Kroon J, van Roon-Mom WMC, Meijer OC. Glucocorticoid receptor antagonist CORT113176 attenuates motor and neuropathological symptoms of Huntington's disease in R6/2 mice. ***Experimental Neurology***. 2024, 374:114675. link

Ma S, Zhang B, LaFave LM, Earl AS, Chiang Z, Hu Y, Ding J, Brack A, Kartha VK, Tay T, Law T, Lareau C, Hsu YC, Regev A, Buenrostro JD. ***Cell***. 2020 1831103-16 link

Matos MR, Visser E, Kramvis I, van der Loo RJ, Gebuis T, Zalm R, Rao-Ruiz P, Mansvelder HD, Smit AB, van den Oever MC. Memory strength gates the involvement of a CREB-dependent cortical fear engram in remote memory. Nature Communications. 2019, 10(1):2315. link

Yamanashi T, Iwata M, Shibushita M, Tsunetomi K, Nagata M, Kajitani N, Miura A, Matsuo R, Nishiguchi T, Kato TA, Setoyama D, Shirayama Y, Watanabe K, Shinozaki G, Kaneko K. ***Scientific Reports***. 2020 10 21629 link

Yang C, Wang Y, Sims MM, He Y, Miller DD, Pfeffer LM. Targeting the Bromodomain of BRG-1/BRM Subunit of the SWI/SNF Complex Increases the Anticancer Activity of Temozolomide in Glioblastoma. ***Pharmaceuticals (Basel)***. 2021, 14(9):904. link

Zayed A, Baranowski C, Compagnion AC, Vernochet C, Karaki S, Cuttoli RD, Saint-Jour E, Bhattacharya S, Marti F, Vanhoutte P, Yaniv M, Faure P, Barik J, Amar L, Tronche F°, Parnaudeau S°. °co-last. ***Nature Communications***. 2022; 13: 1807. link