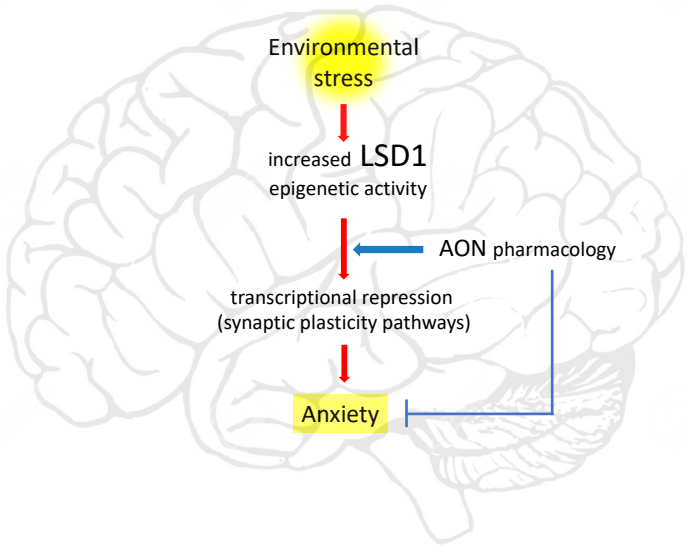
The role of LSD1 as a regulator of homeostatic synaptic plasticity: deciphering a *core* mechanism of social stress response, and its implication in anxiety.

Laboratory of Neuroepigenetics, Elena Battaglioli and Francesco Rusconi

In their many declinations, anxiety disorders represent a significant societal burden. Recent data from the NIMH, estimate the lifetime prevalence of anxiety disorders around 31,1%. One out of three individuals will experience any anxiety disorder at some time in her/his life, critically compromising wellbeing and limiting executive functions. Besides genetic predisposition, social stress represents the main risk factor for anxiety disorders. However, *the comprehension of pathophysiological mechanisms of anxiety and the molecular nature of stress-anxiety relationship* is still tremendously elusive, limiting prognostic efficacy and treatment responsiveness. The hippocampus represents the cerebral hub of anxiety and stress response in mammals. Limiting hippocampal glutamatergic drive through classical anxiolytics (benzodiazepine) temporally ameliorates anxiety symptoms but gradually worsens the disease. On the other hand, antidepressants proved satisfying in a half of treated patients only, suggesting how blunt a weapon these options generally represent.

The candidate will be engaged in the characterization of an epigenetic transcriptional corepressor, Lysine-specific Demethylase 1 (LSD1), shown to limit on demand in response to environmental stress, the expression of synaptic plasticity genes in the glutamatergic compartment. He/she will validate LSD1-regulated pathways as an anxiety-relevant pharmacological target. Recently, our laboratory showed that a mammalian model of increased LSD1 activity significantly shows decreased anxiety-like profile. Furthermore, we recently developed an antisense oligonucleotide (AON)-based pharmacological approach to increase LSD1 activity in the hippocampus that preliminarily showed to reduce anxiety as measured by inherent behavioral paradigms.



The candidate, ideally already expert in most molecular biology techniques and with some experience with in vivo experiments, will have the opportunity to exploit *in vitro* and *in vivo* molecular biology and omics techniques, viral gene delivery to the hippocampus, pharmacological AON administration using preclinical and translational approaches, to understand how LSD1 regulated pathways i) modulate excitatory neurons structural and electrophysiological plasticity, ii) contribute to emotional behaviors and iii) the extent to which their pharmacological modification can be considered as a possible novel treatment for anxiety-based disorders.