LSD1 Scale-Up: transitioning from cells to a pre-clinical RNA-based therapy approach for post-traumatic disorders

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Since its discovery, our research has focused on elucidating the role of Lysine Specific Demethylase 1 (LSD1) in the brain and its implications for complex brain disorders, including neurodevelopmental and neuropsychiatric conditions. LSD1 is an epigenetic enzyme that functions within a larger co-repressor complex, including CoREST and HDAC1/2, to fine-tune the expression of neuroplastic genes in glutamatergic neurons.

Through constitutive genetic manipulation, we demonstrated that LSD1 activity is engaged both in vitro and in vivo in response to homeostasis-demanding paradigms of neuronal activation, such as epileptic and traumatic-like depolarization events. This engagement occurs through the skipping of alternatively spliced exon E8a, increasing LSD1 levels. This response limits synaptic gene expression within a transient post-epileptic/traumatic window, which we hypothesize is crucial for circuit and behavioral preservation. This pathway represents an evolutionary acquisition, exhibiting increasingly complex regulation from mice to humans, with emerging nuances mediated by neuro-specific splicing regulators (including nSR100 and RbFOX1) and long non-coding RNAs such as MALAT1.

We present new evidence implicating the LSD1 pathway, along with its regulators, in resilience biology. We have generated an RNA-based therapy tool designed to transiently boost LSD1 activity, thereby enhancing its co-repressive function within inherent post-traumatic behavioral paradigms and effectively mimicking and strengthening its physiological engagement. Exploiting this tool, we intend to advance our understanding of LSD1 as a modifier of contextual fear memory, the core pathological domain of post-traumatic disorders.