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Therapeutic Potential of Conjugated siRNAs for the Treatment of Major Depressive Disorder

Short Title: Therapeutic Potential of Antidepressant-Conjugated-siRNAs

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Major depressive disorder (MDD) is a severe psychiatric syndrome with very high socioeconomic impact worldwide (Global Burden of Disease Study 2013 Collaborators, 2015). This is attributable to three main factors: *i*) MDD is a highly prevalent disorder in the general population, *ii*) depressive episodes have long duration and occur during active periods of adult life, resulting in very large labor costs, and *iii*) standard MDD treatments have limited efficacy, leaving a high percentage of patients with incomplete responses and poor quality of life, thus increasing suicide risk (Rush et al., 2006).

Based on clinical and preclinical studies, MDD may be associated with altered structural and synaptic plasticity, stress- or immune-related pathology and genetic polymorphisms in brain circuits regulating mood and cognition (Ota and Duman, 2013). In this context, RNA interference (RNAi) may be a useful tool to examine the role of candidate genes in the pathophysiology and treatment of MDD. Hence, RNAi can be used as a therapeutic tool to silence targets involved in the disease process. However, despite its enormous potential, *in vivo* use of RNAi is limited due to the difficulty to deliver sequences of small RNAs (small interfering RNA-siRNA) to the desired neurons/circuits in mammalian brain. Our strategy has been to develop conjugate siRNA molecules (C-siRNA) in which the siRNA sequence was covalently bound to a selective serotonin reuptake inhibitor (SSRI-sertraline) in order to selectively accumulate it by the dense network of serotonin axon terminals in brain. The amounts (typically 0.5-2 nmol/day) of C-siRNA directed against 5-HT_{1A} receptors (5-HT_{1A}-R) or the serotonin transporter (SERT) were then administered intranasally to mice and C-siRNA sequences were localized into raphe serotonin neurons (Bortolozzi et al., 2012; Ferrés-Coy et al., 2016). Using this strategy, we discerned the role of pre- and postsynaptic 5-HT_{1A}-R in the response to stress, the anxiety phenotype and the response to antidepressant treatments. Interestingly, the selective silencing of

presynaptic 5-HT_{1A} autoreceptors was sufficient to elicit antidepressant-like effects in mice thanks to the increased capability of serotonergic neurons to release serotonin during stressful situations (Bortolozzi et al., 2012; Ferrés-coy et al., 2013).

Likewise, we employed this approach to silence SERT expression/function. Intranasal administration of a C-siRNA targeting SERT (C-SERT-siRNA) evoked rapid and robust antidepressant-like responses in mice, including elevated forebrain serotonin levels, presynaptic 5-HT_{1A}-R desensitization, increased hippocampal neurogenesis and expression of trophic factors, and increased dendritic complexity. Further, C-SERT-siRNA reversed depressive-like behaviors in a mouse model of depression. C-SERT-siRNA evoked all these responses in 1 week whereas SSRI fluoxetine required 1 month (Ferrés-Coy et al., 2016). In addition, we are using this strategy to knockdown other genes potentially involved in stress resilience (e.g., TASK-3 channels; Ferrés-Coy et al., unpublished observations) and to target catecholamine neurons, by linking siRNA or antisense oligonucleotide sequences to the respective transporter inhibitors.

Despite the many advantages of siRNA to treat brain diseases, many challenges remain, including off-target effects, rapid degradation, immune response and, poor cellular uptake and selectivity as well as in vivo delivery. Rational design strategies, predictive models based on second-generation algorithms, antibody and chemical modifications and nanocarriers offer significant opportunities to overcome some of the above problems. Although it is still soon to know the impact of RNAi-based therapies on MDD treatment, our approach to deliver C-siRNA sequences to serotonin neurons through the intranasal route has proven successful in order to elicit rapid and robust antidepressant-like actions in rodents, showing a high potential translational value.

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