

Grigorios Papageorgiou¹, Nikolaos Mellios¹⁻²

1.Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM

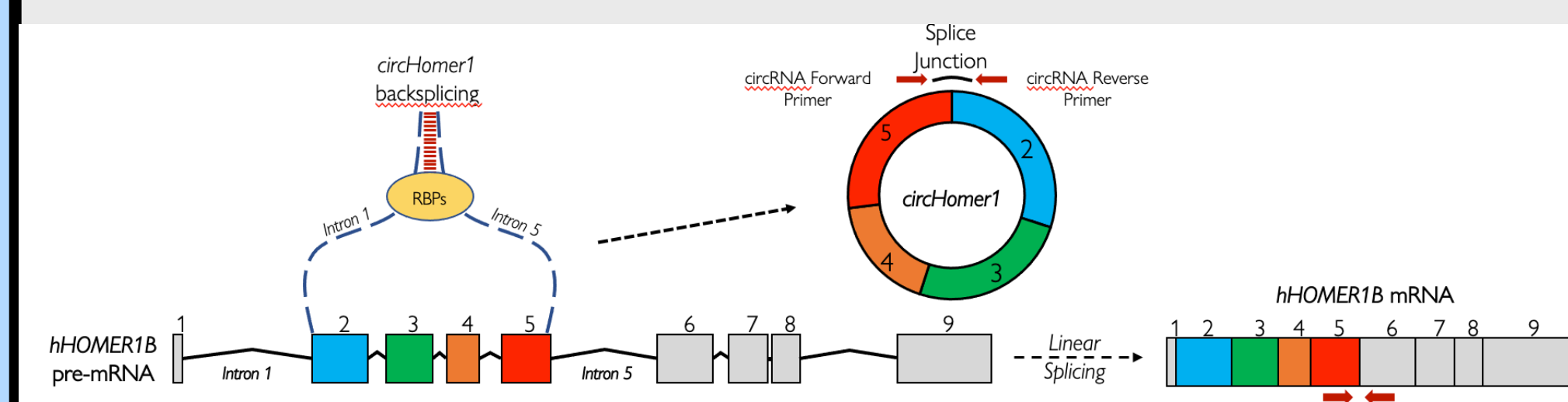
2.Autophagy Inflammation and Metabolism Center of Biomedical Research Excellence, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

INTRODUCTION

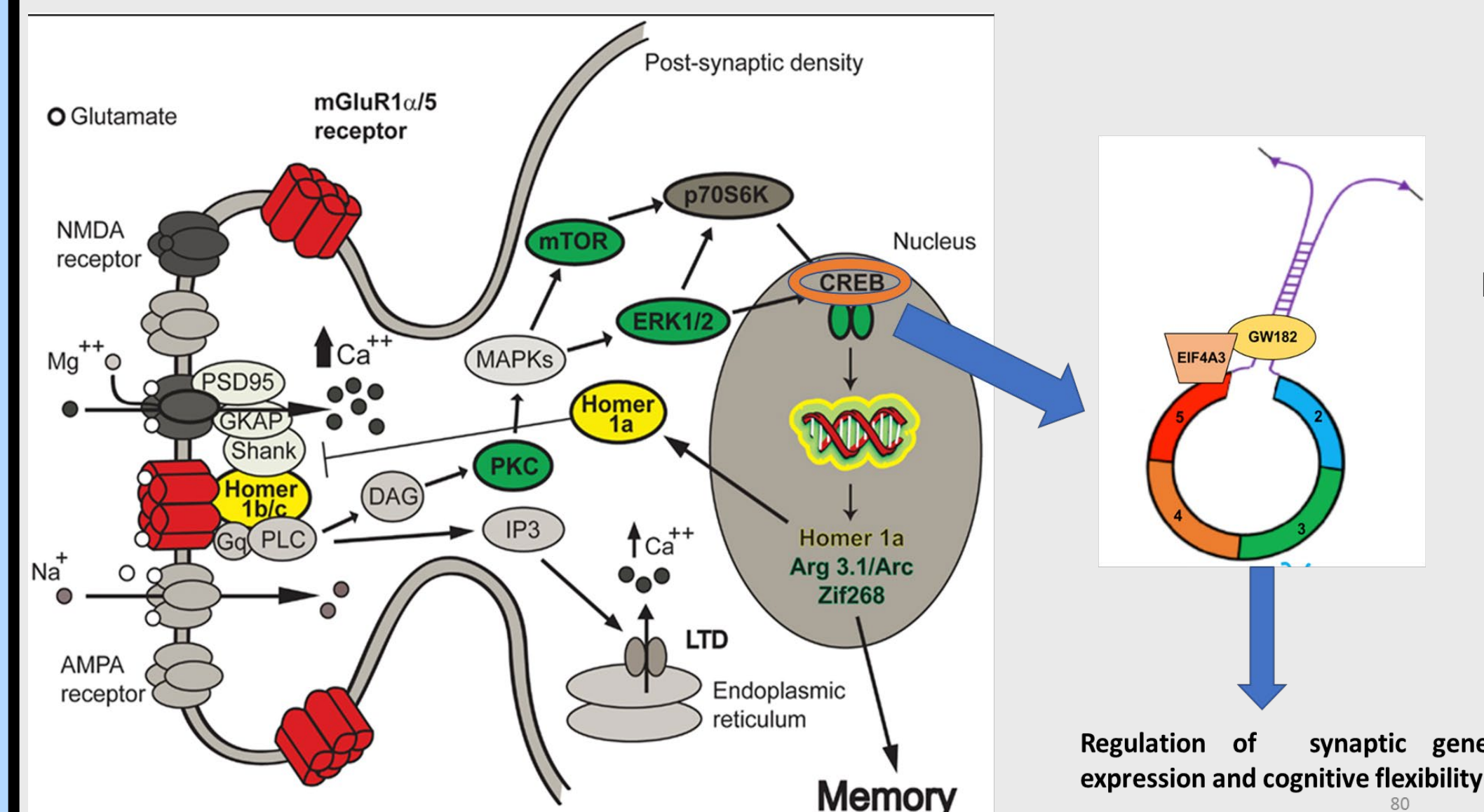
Schizophrenia (SCZ) and Bipolar disorder (BD) are heterogeneous psychiatric disorders that together affect more than 3.5% of the US population. Non-coding RNAs have been shown to play a role in regulating gene expression at the transcriptional and post-transcriptional level and having implications on psychiatric diseases. Circular RNAs are a category of ncRNAs, formed after back-splicing of exons/introns. Homer protein homolog 1 is important for brain functions via regulating glutamatergic synapses, affecting spatial learning and memory and it has been abnormally expressed in psychiatric disorders. *CircHomer1*, is a neuronal-enriched circRNA, derived from exons 2 and 5 of the precursor of the Homer1B mRNA isoform, abundantly expressed in adult frontal cortex, significantly altered in postmortem brains of SCZ/BD patients and *circHomer1* KD is associated with cognitive disturbances.

In my research project, I intend to examine the mechanisms that control *circHomer1* biogenesis within neurons and elucidating the molecular mechanisms that may underlie psychiatric diseases by studying *circHomer1*.

circHomer1 biogenesis



HYPOTHESIS



I hypothesize that RNA binding proteins that could bind to the *circHomer1* splice junction or in the nearby complementary intronic regions, such as EIF4A3 and GW182, could regulate neuronal *circHomer1* biogenesis and that also pharmacological intervention for psychiatric disorders can change *circHomer1* expression profile. Should that be verified, I will test the molecular cascades that underlie its' response to psychiatric treatment.

SIGNIFICANCE-INNOVATION

This study would be the first to attempt to identify the mechanisms that underlie the biogenesis and role of a neuronal circRNA in brain function and psychiatric disorders.

RESULTS

Figure 1: Altered *circHomer1* expression in the frontal cortex of subjects with psychiatric disorders (2 different cohorts)

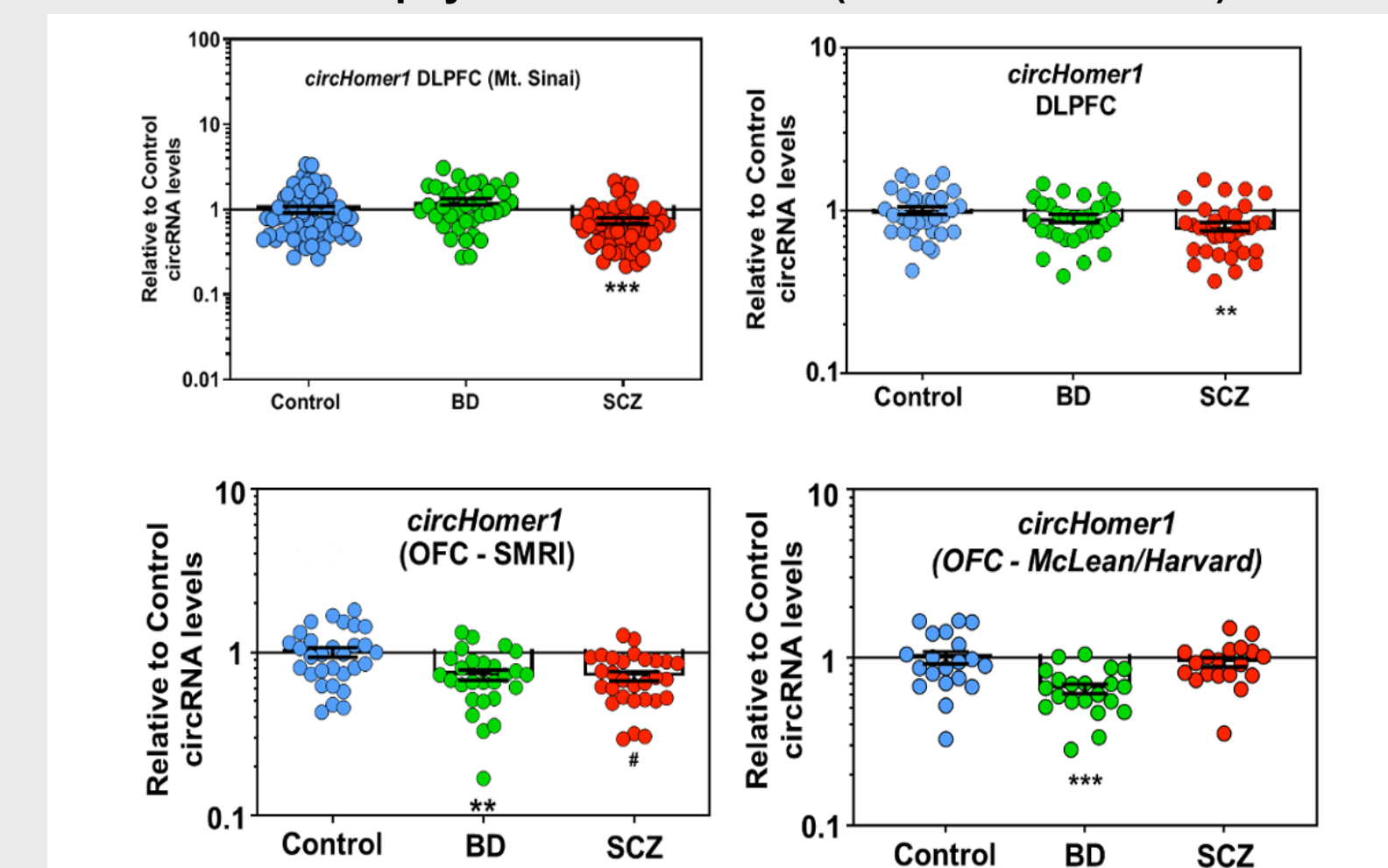


Figure 2: Pharmacological inhibition of eIF4A3 decreases *circHomer1* biogenesis (human and mice conserved)

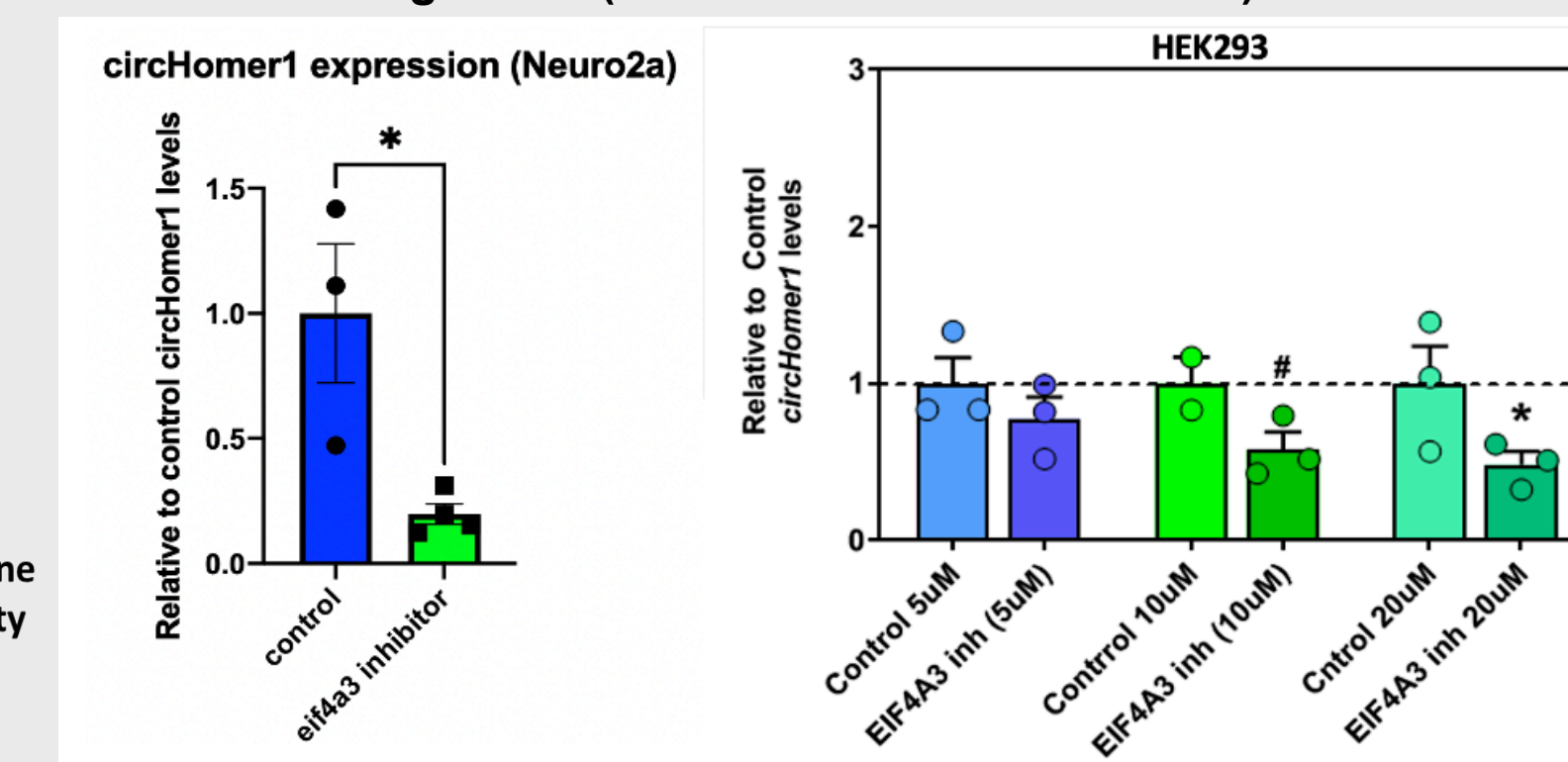


Figure 3: Treatment of neuropsychiatric disorders modulate mouse *circHomer1* levels

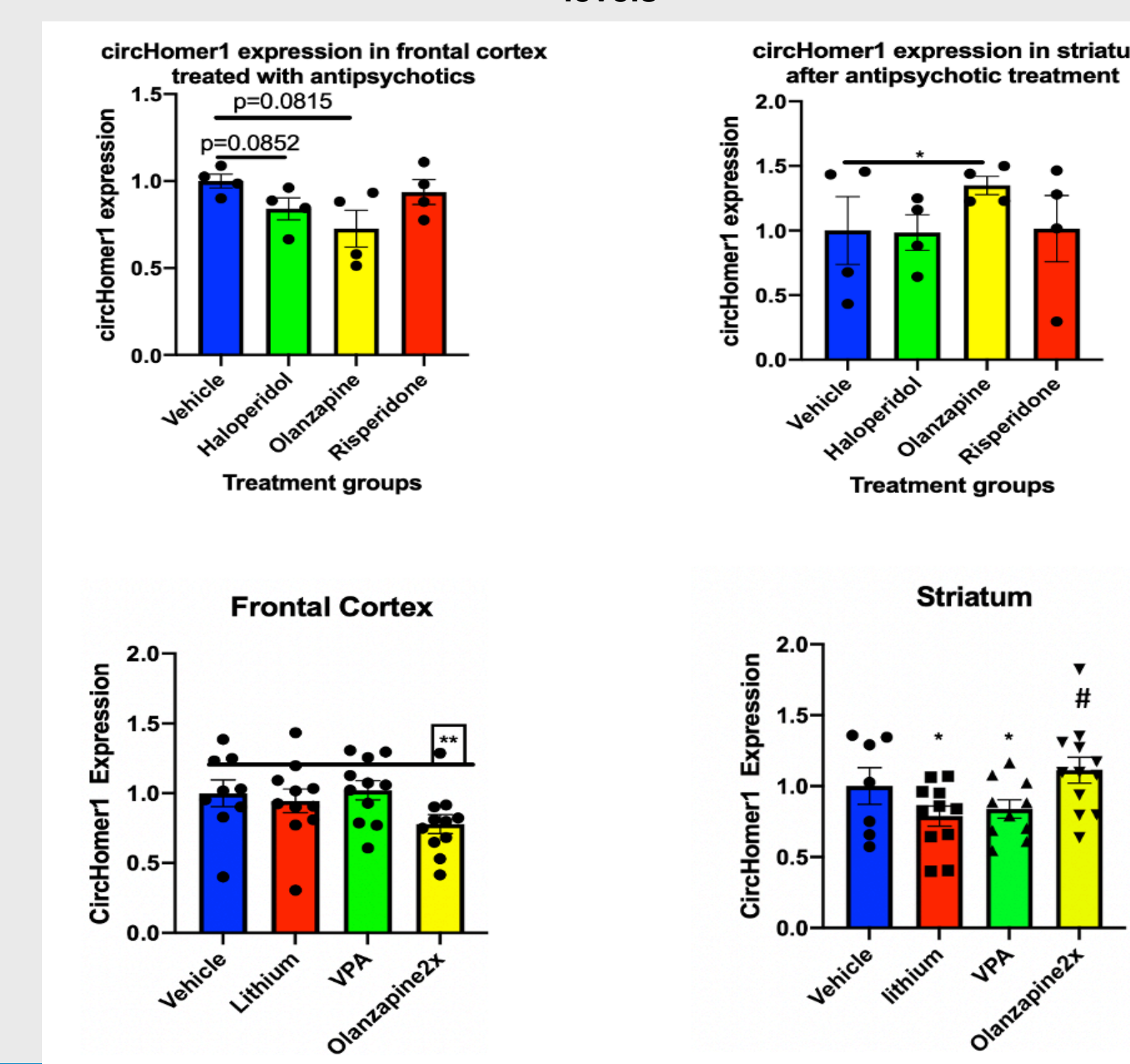
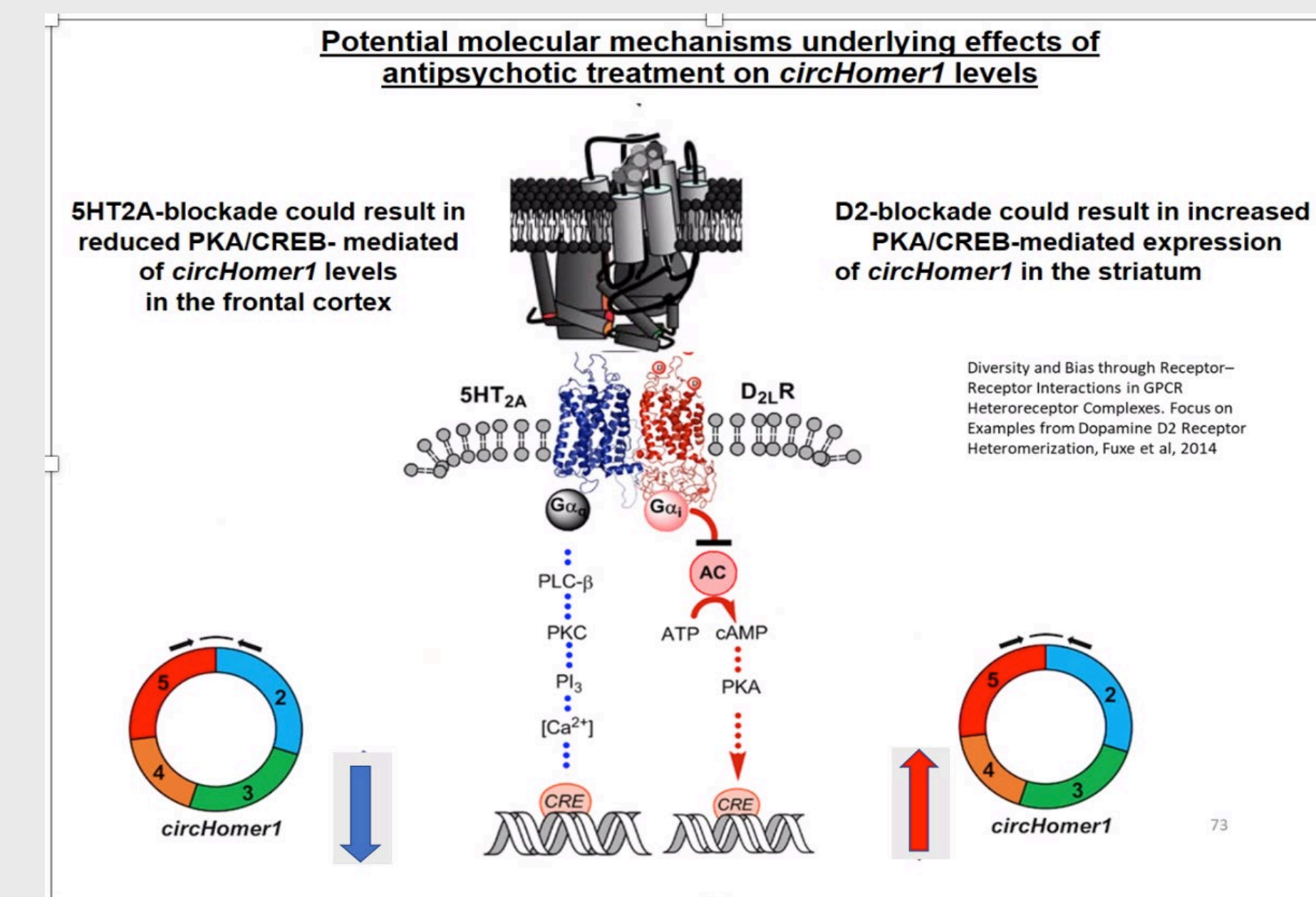


Figure 4: Proposed model of antipsychotics action on *circHomer1* levels



CONCLUSIONS

- eIF4A3 pharmacological inhibition decreases *circHomer1* biogenesis in HEK293 and Neuro2a differentiated cells.
- Pharmacological treatment of neuropsychiatric disorders can modulate mouse *circHomer1* levels in brain regions connected to SCZ/BD pathogenesis

FUTURE DIRECTIONS

1. RNAi and small molecule inhibitor screen to uncover additional RBPs and drugs that could regulate *circHomer1* biogenesis.
2. Test the molecular cascades that underlie the response of *circHomer1* to psychiatric treatment.
3. Study of rodent behavior following antipsychotic treatment

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