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Pharmacobehavioral analysis and transgenic miRNA biomarker reporter zebrafish for high-throughput antidepressant drug discovery

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We have developed a simple compartmentalized zebrafish model of depressive-like behaviors that induces a persistent, severely withdrawn phenotype by separating one fish from a mating group. Isolated fish behavior and expression of miRNAs clinically predictive and responsive to antidepressant treatment were rescued to a normal phenotype by treatment with an antidepressant (Duloxetine or Fluoxetine) or anti-miRNA morpholinos. We conducted limited pathway analysis of neuronal depression-associated transcripts that were affected by compartmentalization which include significant treatment responsive changes to transcription of MAPK/WNT miRNA targets comparable to changes observed *in vitro*, *in clinico* and *in vivo* rodent models. Notably, MAPK8 and PKCB exhibited sex-specific expression asymmetries that were treatment-type specific and may be indicative of mechanisms for common Fluoxetine side effects. These validated miRNA markers have been exploited in transgenic reporter zebrafish lines that glow in response to effective antidepressant treatment, to screen for novel antidepressants using the Keenan Research Centre's one-of-a-kind high-throughput robotic zebrafish screening system.

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