Developing translatable treatments for PTSD in vertebrate and invertebrate pre-clinical models: The adjuvants mirdametinib, D-cycloserine and prediction error disrupt established threat memories

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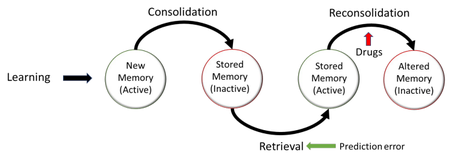
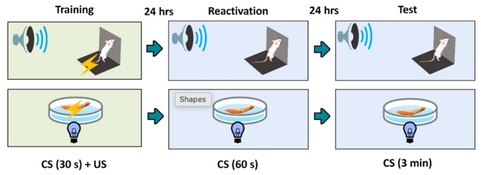
Introduction

- While some patients with Post-traumatic stress disorder (PTSD) recover with existing treatments, many patients experience a return of symptoms or are treatment resistant.
- New treatment solutions and options are needed for PTSD.
- PTSD is characterized by dysfunction of threat memory.
- Targeting memory reconsolidation with clinically translatable drugs and behavioral interventions provides a potential new treatment option.

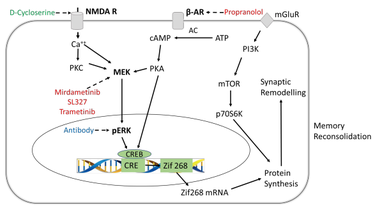
A schematic model of memory storage and re-storage, and its potential inhibition by new clinically translatable PTSD drugs



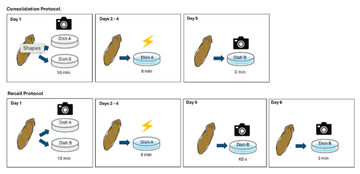
Classical threat conditioning models in rodents and planaria

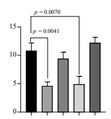


A schematic model of the cellular activity targeted by MEK inhibitors to disrupt memory processes

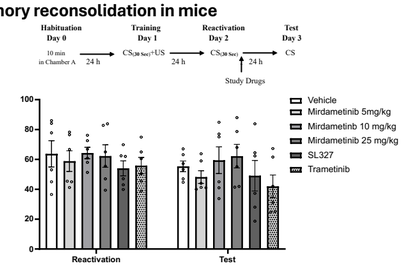


The MEK inhibitor U0126 disrupts threat memory reconsolidation in A planaria invertebrate model

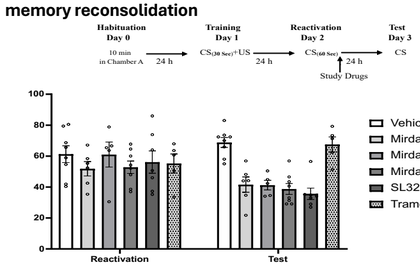




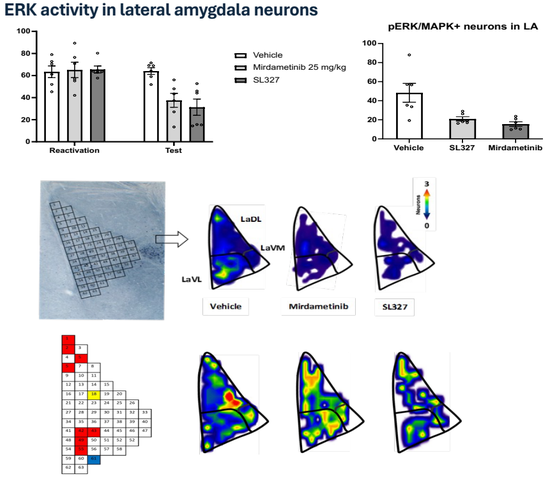
Mirdametinib without prediction error does not disrupt fear memory reconsolidation in mice



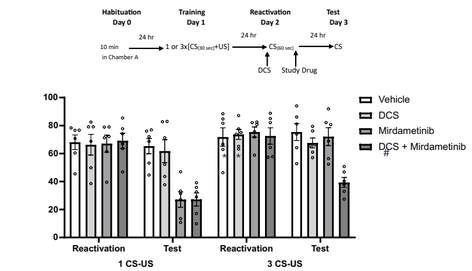
Mirdametinib combined with prediction error disrupts fear memory reconsolidation



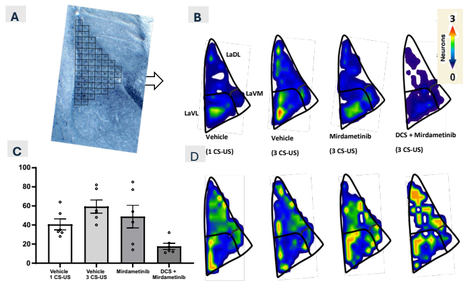
Mirdametinib disrupts fear memory reconsolidation and reduces ERK activity in lateral amygdala neurons

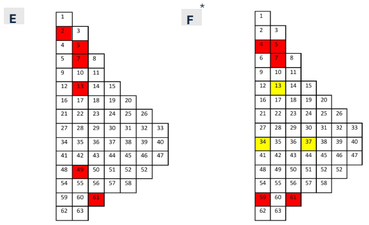


Pre-reactivation DCS enhanced retrieval-induced lability in memories resistant to the effect of mirdametinib on memory reconsolidation

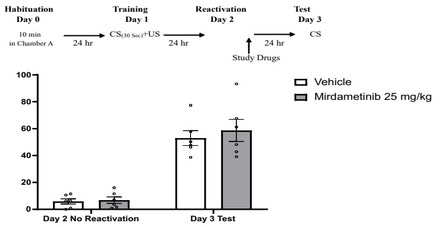


Combination of pre-reactivation DCS with mirdametinib reduces pERK activity in lateral amygdala neurons after strong fear conditioning.

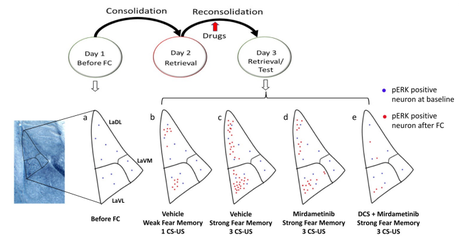




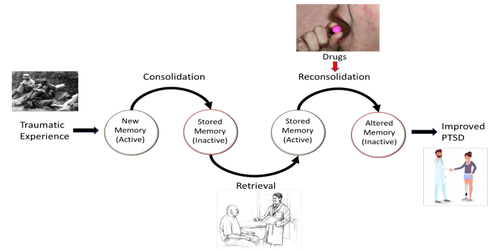
Mirdametinib does not disrupt fear memory reconsolidation in the absence of memory reactivation



A schematic model showing the distribution of pERK-positive neurons in different subregions of LA in different experimental conditions



A schematic model of the clinical application of prediction error and Mirdametinib for treatment-resistant PTSD



Conclusions

- Reconsolidation interference with clinically relevant mirdametinib can disrupt fear memories
- Prediction error is important for destabilisation of fear memories.
- Prediction error has translational potential for disruption of fear memory combined with pharmacological interventions.
- In combination with memory recall Mirdametinib was found to target fear memories without affecting all memory processes.
- A strong fear conditioning protocol rendered a memory trace resistant. However, DCS restored the disruptive effect of mirdametinib.
- Disruption of fear memory reconsolidation is associated with reduction of number of pERK positive neurons in dorsolateral and ventrolateral parts of lateral amygdala.

Conflict of Interest (COI) Statement

The authors report no conflicts of interest

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