Immunophilins in Nervous Regeneration

Michelle G. Patiño,[1] Luciana F. Godoy,[1] Ana B. Ramos Hryb,[1] Mario, D. Galigniana,[1,2] Cristina Daneri Becerra.[1]

[1]Instituto de Biología y Medicina Experimental, IBYME-CONICET

[2] Departamento de Química Biológica, FCEN-UBA

Introduction

Immunophilins (IMMs) are proteins classified as cyclophilins (CyP) when they bind cyclosporine A (CsA), or FK506–Binding Proteins (FKBPs) when they bind the macrolide FK506. The nervous system expresses high levels of IMMs, but their biological roles are poorly understood. Previously, we reported that FK506 favours neurodifferentiation in an FKBP52–dependent fashion, whereas FKBP51 is an antagonistic factor. Organotypic prefrontal brain slices and spinal cord slices treated with FK506 showed high induction of FKBP52 expression, whereas treatments with CsA induced the expression of CyP17 in brain, but not in spinal cord.

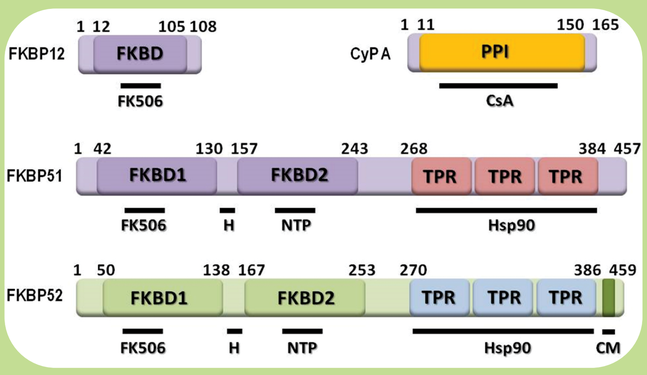
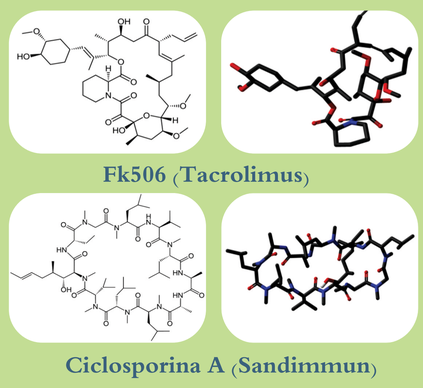


Figure 1: Immunophilins' structure and their domains



Fk506 (Tacrolimus)

Ciclosporina A (Sandimmun)

Figure 2: Structure of drugs that bind to immunophilins

Distance traveled 21 days post injury

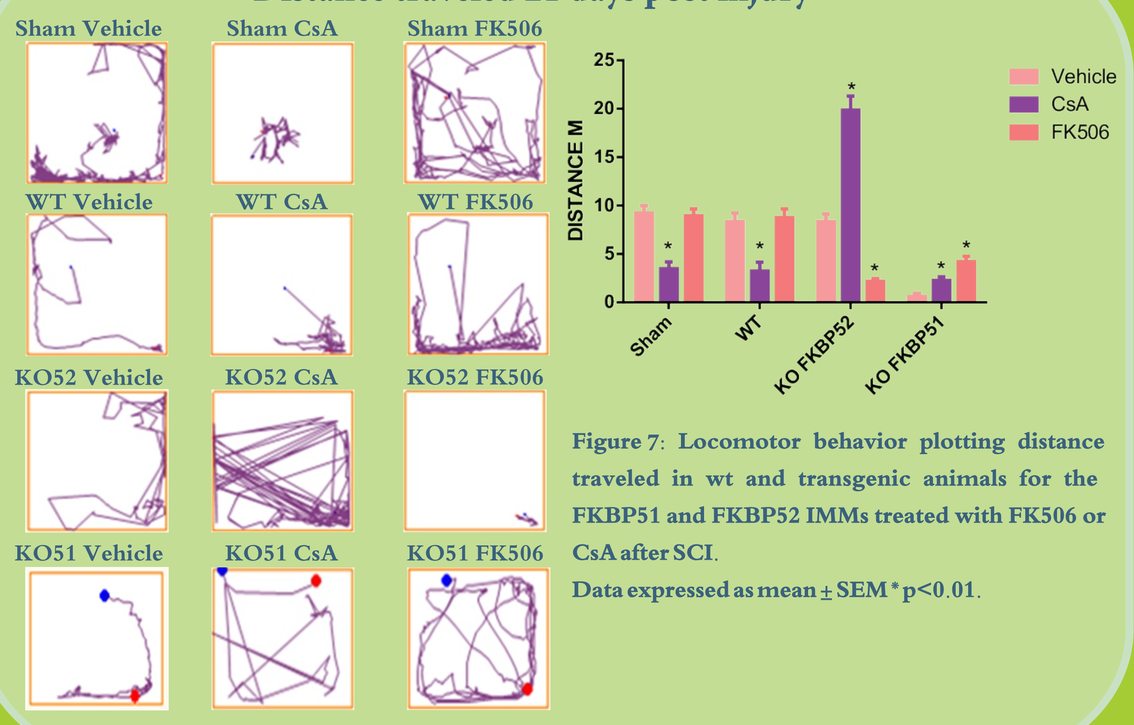


Figure 7: Locomotor behavior plotting distance traveled in wt and transgenic animals for the FKBP51 and FKBP52 IMMs treated with FK506 or CsA after SCI.
Data expressed as mean ± SEM * $p<0.01$.

Results $CoCl_2$

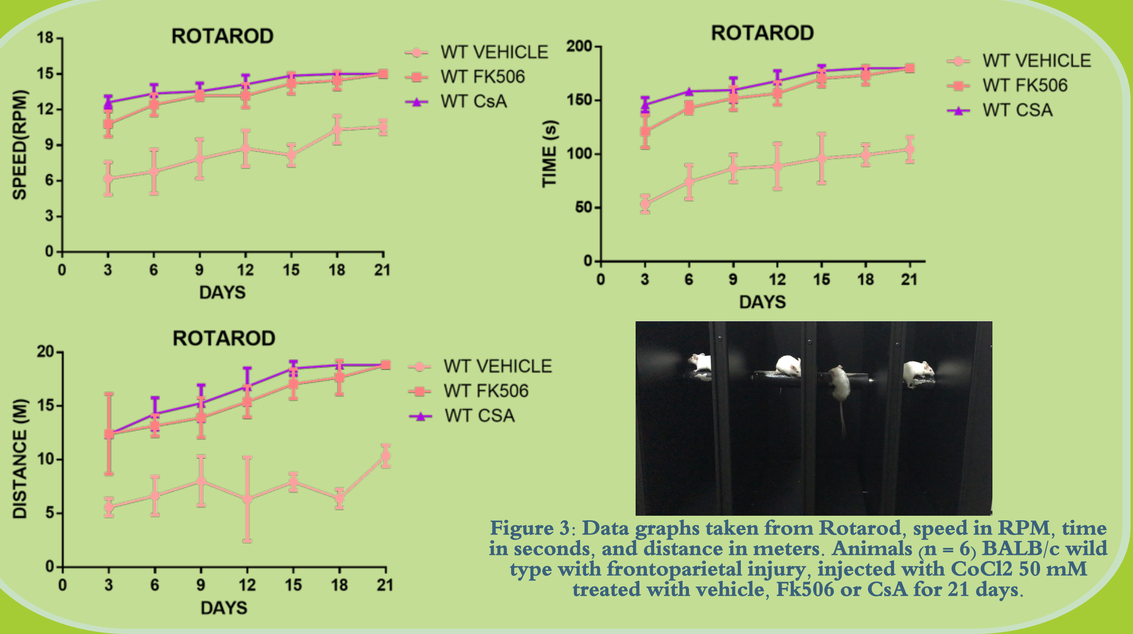


Figure 3: Data graphs taken from Rotarod, speed in RPM, time in seconds, and distance in meters. Animals (n = 6) BALB/c wild type with frontoparietal injury, injected with CoCl2 50 mM treated with vehicle, Fk506 or CsA for 21 days.

ANY–maze video Tracking System

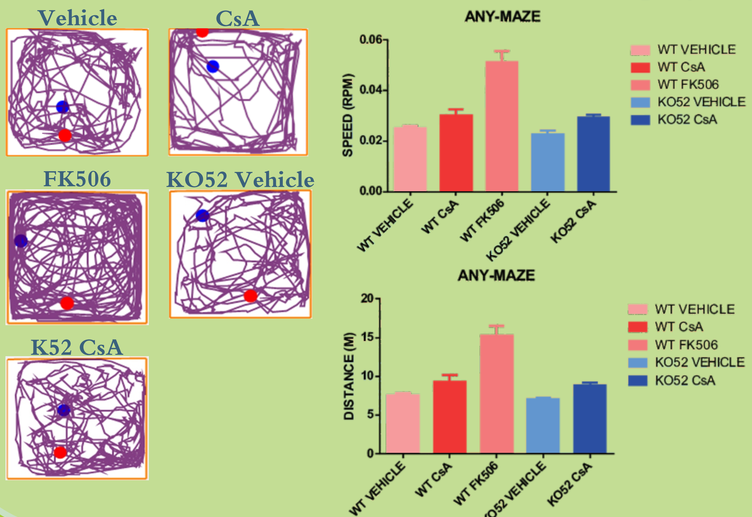


Figure 4: Any–maze program analysis of distance traveled. Images corresponding to 5 minute of footage walk WT, KO FKBP51 and FKBP52 KO Animals with SCI full injury (ME) treated with vehicle, CsA, or 0.01mg/kg of FK506 for 21 days..

Results EC

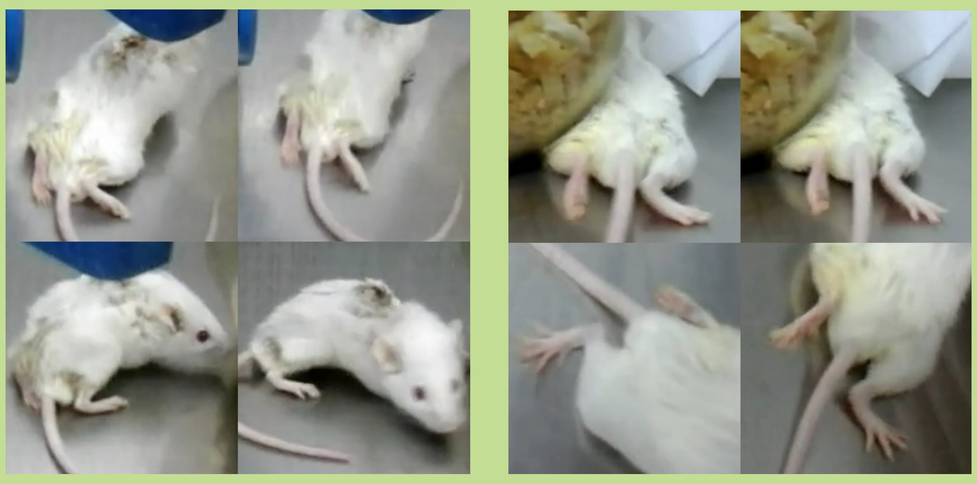


Figure 5: Photographs of WT animals with total spinal cord injury after 9 days of treatment with 0.01 mg / kg of FK506 (left) or CsA (right).

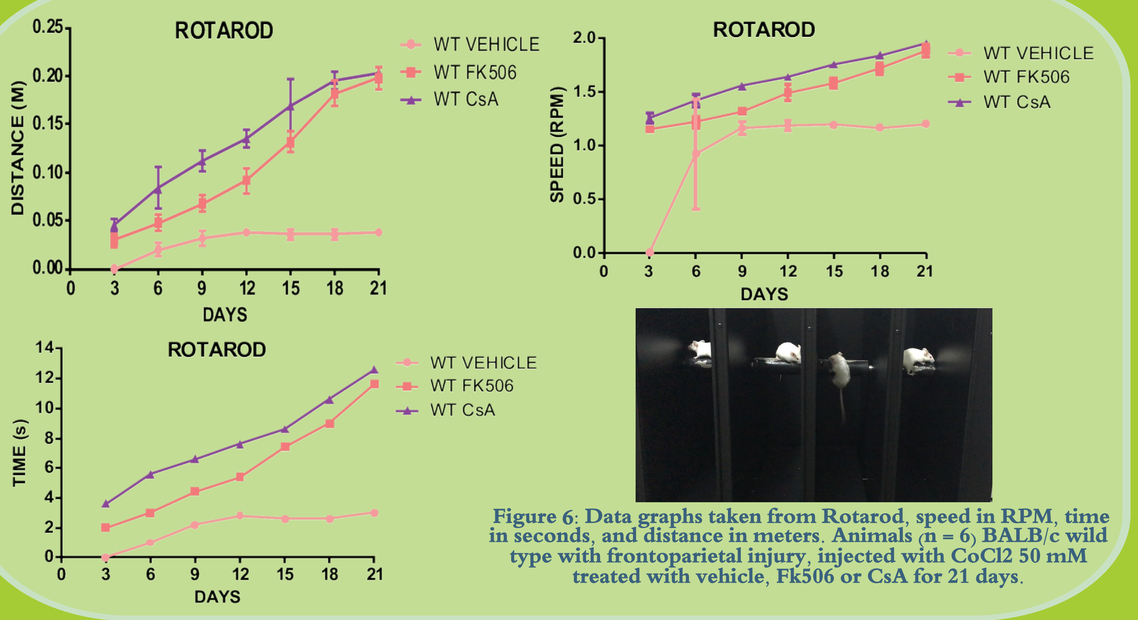


Figure 6: Data graphs taken from Rotarod, speed in RPM, time in seconds, and distance in meters. Animals (n = 6) BALB/c wild type with frontoparietal injury, injected with CoCl2 50 mM treated with vehicle, Fk506 or CsA for 21 days.

Figure 8: Results of the locomotor response through the BMS scale (Basso Mouse Scale) in 21 days of treatment, and bar graph showing comparisons of different groups of animals in three days, chosen with significant differences. Balb / c WT (Wild Type) and KO transgenic mice for FKBP51 and FKBP52 genes, treated with 0.01mg / kg CsA injected subcutaneously (s.c.) daily.

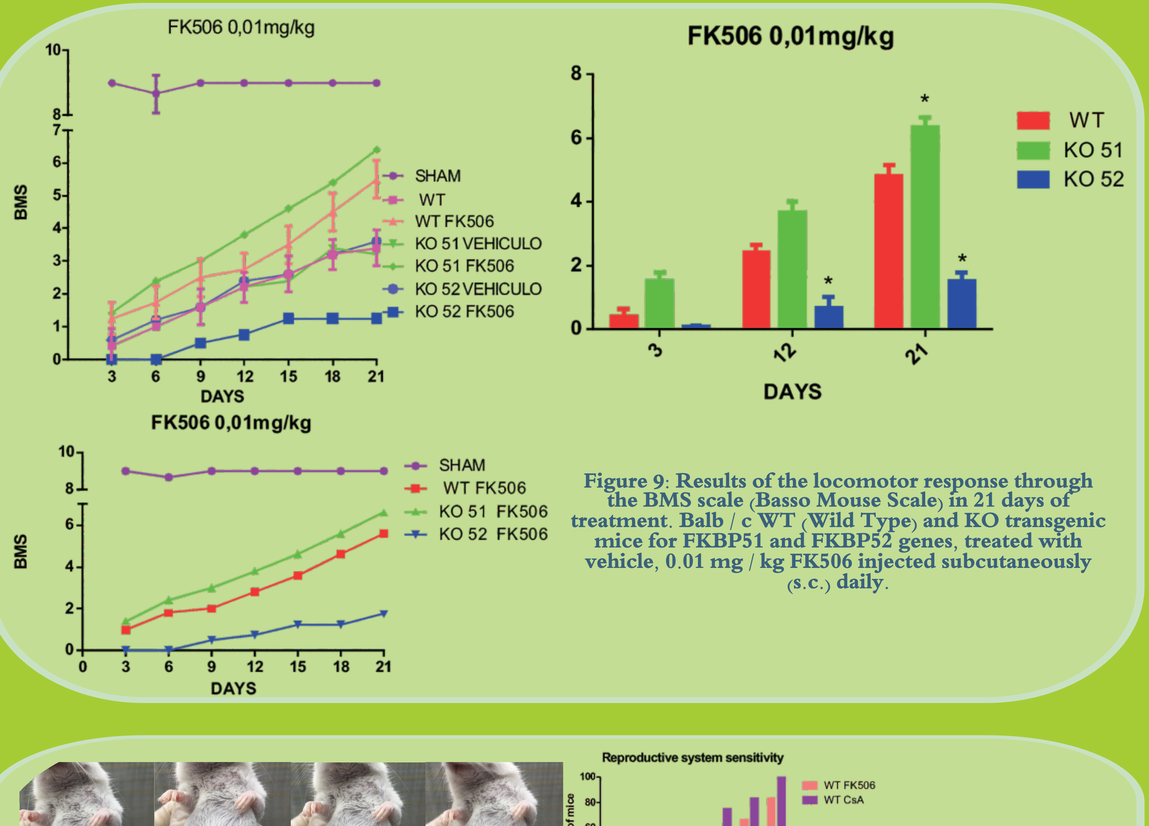


Figure 9: Results of the locomotor response through the BMS scale (Basso Mouse Scale) in 21 days of treatment. Balb / c WT (Wild Type) and KO transgenic mice for FKBP51 and FKBP52 genes, treated with vehicle, 0.01 mg / kg FK506 injected subcutaneously (s.c.) daily.

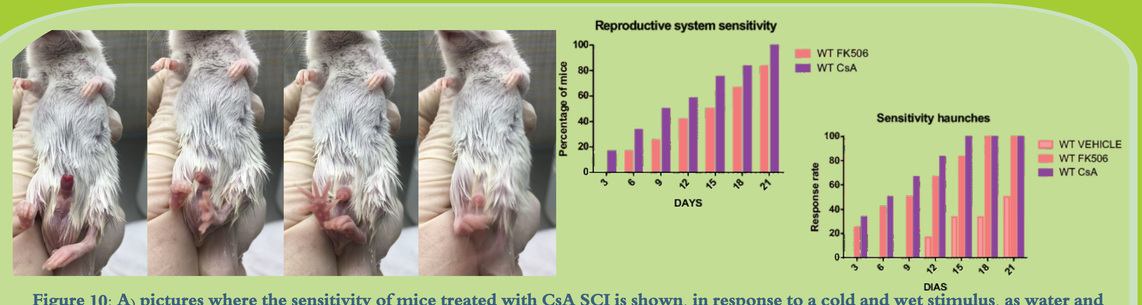


Figure 10: A) pictures where the sensitivity of mice treated with CsA SCI is shown, in response to a cold and wet stimulus, as water and ethanol. B) Images showing reproductive apparatus' sensitivity of CsA–treated SCI mice, accompanied with a motor mobility of the hind legs followed by motility of rear legs. C) Charts in percentage of the number of mice in relation to the response observed in the different days of treatment, with the sensitivity of activation of the reproductive apparatus, and rear legs' sensitivity to cold and wet stimuli (n = 12).

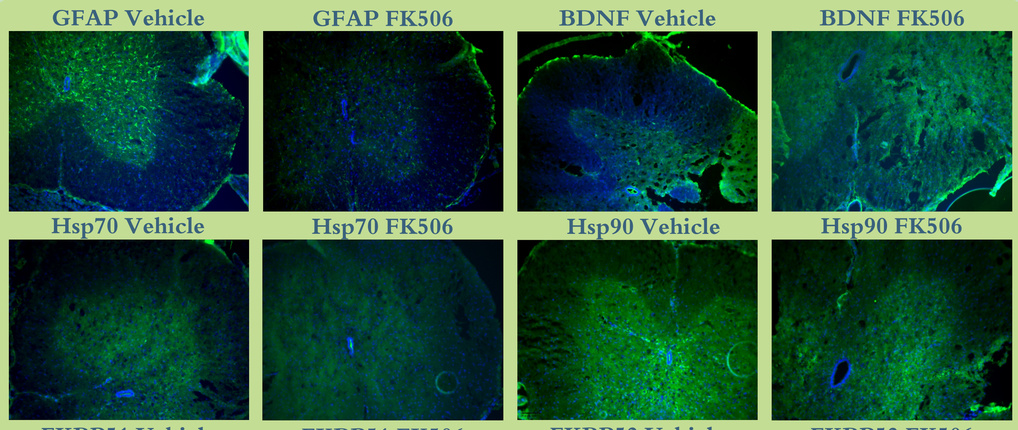


Figure 11: Immunofluorescence of Spinal Cord Injury (SCI) after 21 days of treatment with FK506.

Conclution

We conclude that IMM FKBP52 activated by their specific ligands play key neurotrophic roles.