Tacrolimus (FK506) is a macrolide immunosuppressant, introduced in 90's and approved by FDA for prevention of allograft rejection in solid organ transplantations [1]. Tacrolimus and Cyclosporin A exert their immunosuppressive properties by binding to immunophilins. Immunophilins also called FK506 binding proteins (FKBPs) are prolyl-isomerases that participate in a wide variety of cellular functions including hormone signaling and protein folding [2]. Previous studies on Tacrolimus indicated broad functional roles for the immunophilins in the nervous system.

Unlike Cyclosporine A, Tacrolimus readily crosses the brain-blood-barrier and, thus together with its derivatives, may represent a novel approach to the treatment of neurological disorders [3].

Neuronal effect of Tacrolimus are explained via two different mechanisms; Neuroprotection via reduced NO formation (calcineurin-dependent mechanism) and a fast induction of heat shock proteins [3] and another process called neuroregeneration (via calcineurin-independent mechanisms).Thus, administration of non immunosuppressant ligands for FKBPs was hypothesized to represent important new drugs for the treatment of a variety of neurological disorders [1]. Animal study proved accelerated neuroregeneration after oral administration of a non immunosuppressant FKBP-12 ligand in rats [4].

The neuroregenerative property of Tacrolimus was believed to depend on the 12-kDa FK506-binding protein (FKBP-12). Another study suggested that the neuroregenerative properties of Tacrolimus and steroid hormones are mediated by disruption of steroid-receptor complexes. It remained unclear which component mediates neurite outgrowth, although the most likely candidates were FKBPs, hsp-90, and p23 [5]. Gold BG et al. designed a study on human neuroblastoma SH-SY5Y cells, and proved that Immunophilin FKBP-52 (and not FKBP-12) mediates the neuroregenerative action of Tacrolimus. In these cells, the neuroregenerative action of Tacrolimus (10 pM to 10 nM) was completely prevented by the addition of a monoclonal antibody (50-100 nM) to the immunophilin FKBP-52 (also known as FKBP-59 or heat shock protein 56), a component of mature steroid receptor complexes [6].

This neuroregenerative aptitude of FK506 can be applied as a favorable pharmacologic potential, for selecting tacrolimus as the post-transplant immunosuppressant of choice for those who suffer from neurodegenerative disorders as well as end stage organ failure.

Further studies, especially double-blind, placebo-controlled clinical trials on human allograft recipients who suffer a neurodegenerative disorder should be designed to study the neuronal effects of tacrolimus on human subjects.

References