

Neuroimmunophilin Ligands

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In the early 1990s, reports from the laboratories of Solomon Snyder and Bruce Gold suggested that the immunosuppressant drug FK506 possessed neuroprotective and neuroregenerative properties. FK506 promoted neurite outgrowth from neuronal cultures *in vitro*, and enhanced recovery of sciatic nerves in rats following lesioning. FK506 exerts its immunosuppressant effects by binding to the 12 kilodalton FK506-binding protein (FKBP12) and subsequent inhibition of the phosphatase calcineurin by the FKBP-FK506 complex. Subsequently, scientists at Guilford Pharmaceuticals demonstrated that the neuroregenerative effects resided in the FKBP binding domain portion of FK506, and that nonimmunosuppressant analogs of FK506 could be designed that retained the neuroprotective and neuroregenerative effects of FK506.

Stuart Schreiber, who elucidated the immunosuppressant mechanism of FK506 15 years ago, coined the term “immunophilins” to denote proteins such as FKBP12 and cyclophilin A that bind immunosuppressant drugs and mediate their actions. Immunophilins such as FKBP12 are highly expressed in the mammalian brain, and we have termed these CNS-residing proteins the neuroimmunophilins. Several structural classes of small molecule FKBP ligands have been synthesized and studied, and these will be reviewed. The effects of representative compounds *in vitro* and *in vivo* will be discussed.

FKBP ligands such as GPI 1046 promote neurite outgrowth from dorsal root ganglion cultures *in vitro*. GPI 1046 and numerous other compounds have been shown to significantly restore striatal dopaminergic nerve function following lesioning of mouse brain by the neurotoxin MPTP. These effects are observed both when the drugs are given concomitantly with the toxin (suggesting a protective effect) and when given after toxin-induced lesioning (suggesting a regenerative component of action). These results were subsequently replicated in primates.

The penile cavernous nerve has also been shown to respond to compounds such as GPI 1046. Compounds such as GPI 1046 provide neuroprotection for penile innervation from degeneration following nerve crush injury in rats. Rats were treated with GPI 1046 just prior to having their right cavernous nerves crushed with forceps. Intracavernosal pressure responses to electrostimulation of the right (injured) and left (intact) cavernous nerves were recorded for each animal at 24 hours or 7 days post surgery. The right and left major pelvic ganglia were processed for neuronal nitric oxide synthase (NOS) immunoreactivity. Animals treated with either FK506 or GPI 1046, as compared to untreated animals, showed nearly complete protection of NOS neurons following the lesion, and maintenance of intracavernosal nerve pressure. These results suggest that administration of neuroimmunophilin ligands (NILs) may protect the penile cavernous nerve from traumatic damage such as that caused by prostate surgery.

Based on the results described above, Guilford Pharmaceuticals is currently in two Phase II clinical trials with a second generation NIL, GPI 1485, for Parkinson’s Disease and erectile dysfunction following radical prostatectomy.