Preface

The most widely used immunosuppressant drug therapy in organ and neural transplantation is cyclosporin-A(CsA). CsA was isolated from soil fungus in 1976, and was shown to block T-cell proliferation by inhibiting cytokine transcription via binding to calcium-calmodium-dependent phosphatase, calcineurin (Figs. 1 and 2). CsA was subsequently marketed by Sandoz Pharmaceuticals Inc. in 1979. To date, there are 250,000 organ and 300 neural transplant recipients who have benefited form CsA adjunctive treatment. Though structurally different, another calcineurin inhibitor FK-506 (also known as tacrolimus) has been shown to produce similar immunosuppressive effects. Over the last five years, accumulating evidence suggests that both CsA and FK-506 can be neuroprotective, in addition to their primary immunosuppressive effects (Table 1 and Fig. 3). Although mainly used as immunosuppressants, newly identified nonimmunosuppressive properties of CsA and KF-506 suggest their potential as therapeutic agents for neurological disorders. Four major CNS actions of CsA and FK-506 could promote neuropro-tection. First, inhibition of calcium-phosphatase calcineurin by these immunosuppressants can prevent calcium-dependent enzyme disturbances and can reduce nitric oxide production. Because calcium channel blockers and nitric oxide synthase inhibitors have been shown to alleviate neurobehavioral deficits in models of neurological disorders, similar beneficial effects may be rendered by these calcineurin inhibitors. Second, blockade of the mitochondrial permeability transition pore (which is an inducer of cell death) by these immunosuppressants has been shown to retard neurodegeneration. Opening of the mitochondrial permeability transition pore triggers release of apoptotic factors that can initiate cascades leading to cell death. Such upregulation of apoptotic markers has been noted in many neurological disorders. Accordingly, this inhibition of the opening of the mitochondrial permeability transition pore can block apoptotic cell death. Third, CsA and FK-506 can promote neurotrophic factor support. In primary cultures of dopaminergic cells, enhanced elongation of neurites was observed after treatment with immunosuppressants or their analogs. Similar neurite outgrowth or regrowth following exposure to immunosuppressants has been noted in normal or damaged sciatic, cortical cholinergic, and serotonergic neurons. Immunosuppressant treatment thus offers neurotrophic factor support to many neurotransmitter

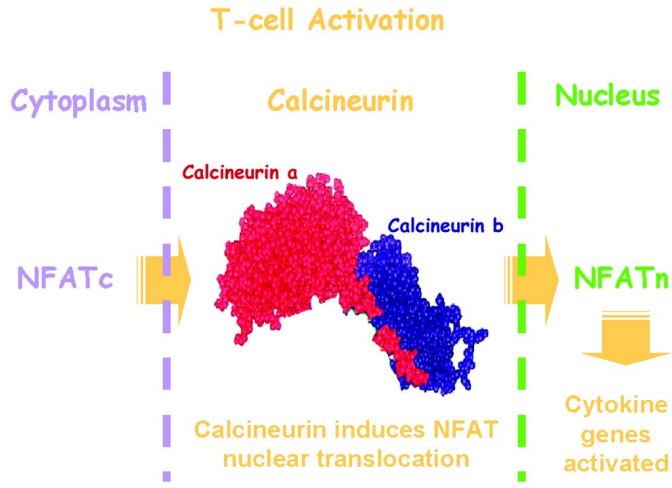

Fig. 1. T-cell activation. Nuclear factor of activated T-cells (NFGAT) predominantly resides in the cytoplasm (NFATc), and is translocated into the nucleus via calcium/calmodulin-dependent serine/threonine phosphatase, calcineurin (composed of a catalytic subunit called calcineurin A, and a regulatory subunit calcineurin B). Once NFAT reaches the nucleus (NFATn), cytokine genes are activated, resulting in IL-2 production during T-cell activation.

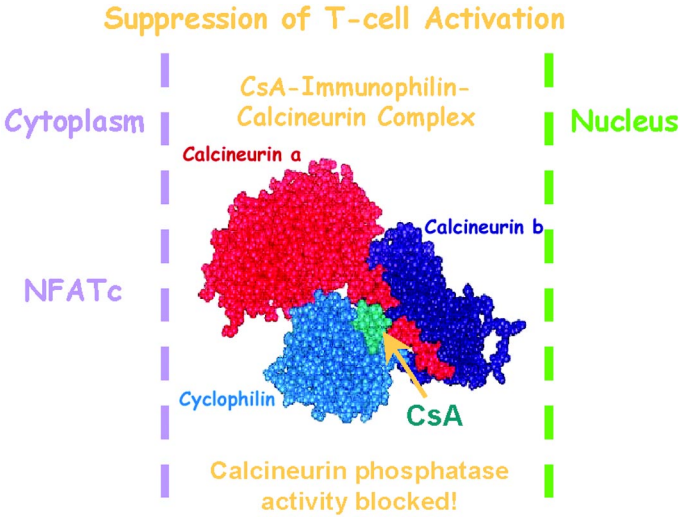

Fig. 2. Suppression of T-cell activation. Calcineurin is the target of immunosuppresive drugs CsA and FK-506. When an immunosuppressive drug binds with its specific immunophilin and the calcineurin complex, NFAT cannot translocate from the cytoplasm into the nucleus. Accordingly, the blockade of the calcineurin phosphatase activity leads to suppression of T-cell activation.

Table 1
Neural Actions of Immunosuppressants and Their Analogs

Inhibition of calcineurin
Blockade of mitochondrial permeability transition pore opening
Promotion of neurotrophic factor effects
Scavenging of free radicals

Note. Accumulating evidence in recent years suggests that immunosuppressants and structurally similar drugs can modulate CNS functions, which may promote neuroprotection, in addition to their primary immunosuppressive functions.

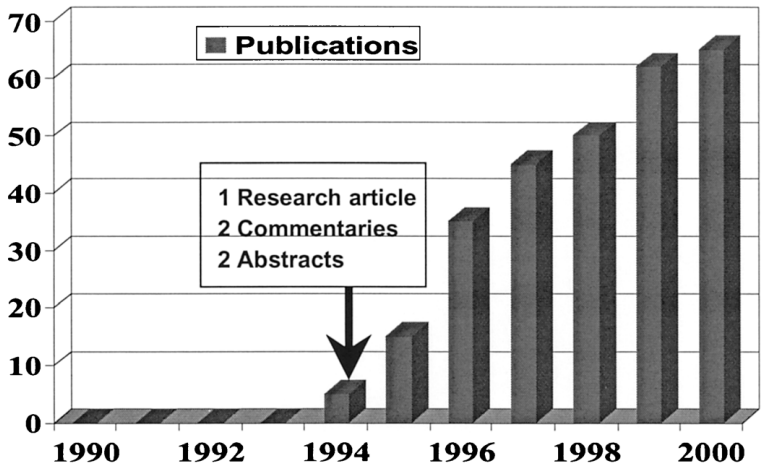

Fig. 3. Scientific literature, 1990–2000. Neuroprotective effects of immunosuppressants and their analogs have recently been demonstrated, with a surge in peer-reviewed publications over the last five years.

systems. Fourth, immunosuppressants or structurally similar drugs can block formation of free radicals, thereby inhibiting lipid peroxidation. Because free radical scavengers have been shown to protect against models of neuronal death, the potential of these drugs to prevent increased production of free radicals may lead to similar protective effects. Though it is not clear whether these factors initiate events causing cell death or consequences of the disease process, experimental therapeutic efforts aimed at preventing or at least delaying disease progression by blocking calcium channels, restoring mitochondrial energy metabolism, providing neurotrophic factors, and scavenging excess free radicals have shown beneficial effects. In this regard, CsA and FK-

506, by targeting calcium channels and the mitochondria permeability transition pore, promoting neurotrophic factor support, and inhibiting free radicals may be considered multiple site-of-action therapeutic drugs.

The observations that immunophilins and structurally similar ligands possess neurotrophic and neuroprotective properties in addition to their immunosuppressive effects suggest that immunosuppressant therapy may have dual beneficial effects for transplant recipients by promoting graft survival and function, as well as inhibiting graft rejection. *Immunosuppressant Analogs in Neuroprotection* focuses on recent preclinical evidence that demonstrates neurotrophic/neuroprotective effects of immunosuppressants when administered alone or when combined with neural transplantation therapy in animal models of neurological disorders. The Foreword by Drs. Snyder and Aghdasi introduces the reader to the evolution of immunosuppressants as neuroprotective agents, and discusses the impetus for developing immunosuppressant analogs, called neuroimmunophilins, as neuroprotective agents for neurological disorders. Part I (Chapter 1: Introduction, Keep et al.) provides the scientific rationale for initiating investigations into the neurotrophic/neuroprotective effects of immunosuppressants. The succeeding chapters are then divided into six sections that correspond to specific animal models of neurological disorders.

Part II deals with the use of immunosuppressants and similar drugs without immunosuppressive primary action in Parkinson's disease animal models, including MPTP and 6-OHDA (Chapter 2, Ogawa and Tanaka). Because differential positive effects of immunosuppressants have been attributed to minimal access of these compounds to cross the blood–brain barrier, a chronic and a high dosage (>10 mg/kg) drug treatment coupled with a compromised blood–brain barrier may be needed to promote the neuroprotective effects of immunosuppressants. However, high dosage and chronic immunosuppressant regimens produce such negative side effects as nephrotoxicity and hallucination among others. Analogs of immunosuppressants have been developed to avoid these risk factors including elimination of the immunosuppressive property of the drug, but retaining its neurotrophic feature. These non-immunosuppressant analogs, neuroimmunophilins are discussed in detail in Chapters 3 (Costantini and Isacson) and 4 (Steiner et al.). The effects of immunosuppressants in parkinsonian animals that have received dopaminergic transplant are discussed in detail in Chapter 5 (Castilho et al.). The blockade of the mitochondrial permeability transition pore and how it relates to the protective effects of immunosuppressants in Parkinson's disease are presented in Chapter 6 (Korlipara and Schapira).

Most neurological disorders are characterized by cognitive dysfunctions, in addition to motor abnormalities. Part III presents laboratory findings showing the therapeutic efficacy of drugs resembling immunosuppressants or even immunosuppressants themselves in two major neurological disorders, namely Alzheimer's disease (Chapter 7, Mattson) and Huntington's disease (Chapter 8, Leventhal and Kordower).

Neurological disorders may be characterized by progressive neurodegeneration, as tackled in Parts II and III. Other neurological disorders are characterized by severe brain insults, such as stroke and traumatic brain injury, and are accompanied by more debilitating effects. Part IV provides evidence of similar beneficial effects of immunosuppressants in animal models of stroke (Chapter 9, Gogvadze and Richter; Chapter 10, Wakita and colleagues; Chapter 11, Ogawa and colleagues; Chapter 12, Sharkey and colleagues), and traumatic brain injury (Chapter 13, Okonkwo and Povlishock).

Part V provides positive effects of immunosuppressants in spinal cord injury (Chapter 14, Ibarra and Diaz-Ruiz; Chapter 15, Palladini and Caronti); Part VI presents their utility in sciatic nerve injury (Chapter 16, Gold; Chapter 17, Steiner et al.); Part VII discusses potential use of immunosuppressants in other disorders of the central nervous system (ALS: Chapter 18, Keep et al.; Drug addiction: Chapter 19, Watanabe).

Although we have categorized the chapters according to the type of neurological disorders that the authors have used to demonstrate beneficial effects of immunosuppressants and/or their analogs, most of the chapters offer novel hypotheses on the mechanisms of neuroprotection. For example, Chapters 6, 9, 13, and 18 support the blockade of mitochondrial permeability transition pore hypothesis, Chapters 2–5, 12, and 15–17 provide proof of neurotrophic effects, and Chapter 13 proposes the free radical scavenging effects of immunosuppressants. In addition, one may note that chapters dealing with CsA or FK-506 (2, 5, 6, 8, 10, 11, 13–16, and 19) demonstrate the therapeutic efficacy of these immunosuppressants based on their unique property of inhibiting calcineurin, whereas chapters on neuroimmunophilin (3, 4, 12, 17, and 18) argue that calcineurin inhibition (i.e., immunosuppressive property) is not necessary for neuroprotection.

These preclinical observations indicate that CsA and FK-506, and their analogs, exert neuroprotective effects on their own. In addition to providing immunosuppression to the transplanted tissues, immunosuppressants may also enhance the survival of the grafts and the damaged host tissue via their trophic factor effect and other survival-promoting features. We have pointed out above that neuroprotection with immunosuppressant treatment may only

be consistently achieved with chronic and high doses and a compromised blood–brain barrier. The advent of immunosuppressant analogs, such as the neuroimmuno-philins, may be an equally potent alternative to deliver these agents into the central nervous system and one that can promote neuroprotection.

The goal of *Immunosuppressant Analogs in Neuroprotection* is to advance the use of immunosuppressants and their analogs as a new breed of neuroprotective agents. Because the majority of these agents have been used in the clinic as immunosuppressants for many years now, we believe that their new clinical application as neuroprotective agents will be expedited, such as other experimental drugs (e.g., antioxidants, anti-apoptotic agents, bioenergetic supplements, etc.) used for the treatment of neurological disorders.

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