The pathophysiology after radical prostatectomy involves among other things neural injury [1]. Even in nerve-sparing surgery, manipulation, traction, and stretching of the cavernous nerves occurs, leading to a variety of sequelae such as apoptosis of smooth muscle and endothelium, reduction in the density of nerves staining for nitric oxide synthase, up-regulation of fibrogenic cytokines such as transforming growth factor β, and smooth muscle fibrosis and loss [2,3]. Added to this, the chronic absence of erection secondary to cavernous nerve neuapraxia results in failure to achieve cavernosal oxygenation with the potential for further structural damage to the cavernosal smooth muscle [4].

Pharmacologic neuromodulation, the concept that medications can be used to either protect or regenerate nerves exposed to trauma, is far from new [5]. For over a decade such a concept has been explored, albeit in animal models. In tibial, facial, and sciatic nerve injury models a number of agents have been shown to effect neuromodulation. These agents include immunophilin ligands, rapamycin, minocycline, and erythropoietin. The class of agents most studied is that of immunophilin ligands, a group of agents, including cyclosporine and FK506 (also known as tacrolimus), a group of agents that bind to immunophilin ligands, and cellular signaling proteins present in immune and neural tissue [6]. At this time the means by which these agents affect neuromodulation has not been fully elucidated.

The great drawback to immunophilin ligands is that the currently available agents are immunosuppressant in nature. It has, however, been shown that doses of FK506 used in humans with rheumatoid arthritis (typically 2–3 mg/d) do not induce immunosuppression (as opposed to the 5-mg daily dose used in patients after transplantation procedures) [7]. In an effort to circumvent the concerns regarding immunosuppression, a series of non-immunosuppressant immunophilin ligands have been developed by Guildford Pharmaceuticals (now known as MGI Pharmaceuticals), known by their GPI prefix, and by Astellas Pharmaceuticals (the manufacturer of FK506), which has developed and explored FK1706, a non-immunosuppressant immunophilin ligand, in animals.

The paper by Valentine et al [8] is an exciting extension of work that this group has done in this area over the past 5 yr. In a rat model of cavernous nerve crush injury, which is well-established as a means of studying the functional and structural sequelae of cavernous nerve injury (and which is believed to be somewhat representative of the neural injury that occurs at the time of radical prostatectomy), the investigators studied the impact of GPI-1046 (a non-immunosuppressant immunophilin ligand) orally and intraperitoneally, as well as FK506 intraperitoneally, on erectile function recovery (measured by intracavernosal pressure generation in response to cavernous nerve stimulation) and cavernous nerve architecture.
using transmission electron microscopy. They have shown that both oral and intraperitoneal administration of GPI-1046 results in similar erectile function recovery to that of FK506 in both unilateral and bilateral cavernous nerve-injured animals following short-term (1 d) and medium-term (7 d) administration of these agents. Furthermore, they have demonstrated significant preservation of cavernous nerve architecture, with prevention of axonal degeneration in 83% of unmyelinated axons.

A number of points are worth mentioning. In the United States clinical trials have completed enrollment for studies analyzing the effect of FK506 and the non-immunosuppressant immunophilin ligand GPI-1485 in the radical prostatectomy population. The medications have been administered prior to surgery and for a 6-mo period postoperatively. It is of interest that the Valentine study assessed GPI-1046, a different agent, and the exact applicability of this agent to the human model is unclear. The greatest drawback to the GPI compounds is that, to the best of my knowledge, they are not approved for human use by regulatory agencies (outside of clinical trials) and thus even if animal and human data demonstrate a potential role for them in the radical prostatectomy population, their availability will be years away.

The reader must exercise caution in attempting to compare the relative neuromodulatory capabilities of GPI-1046 and FK506 based on these data because it remains unclear how closely correlated animal and human pharmacokinetics are for these agents. Furthermore, in our laboratory we have demonstrated that the dose of FK506 most effective in preserving erectile function and cavernous nerve structure in an identical animal model is 3.2 mg/kg (Golijani et al, presented at American Urological Association, 2006). Of note, animals exposed to >5 d of FK506 tend to lose their ability to gain weight and in previous experiments from the Johns Hopkins group, some animals have died secondary to chronic, high-dose FK506 administration [9].

It is difficult to believe that we will not have neuromodulatory drugs available to us in the future. Think of the widespread applicability that they would have; even aside from radical pelvic surgery in men and women, it is possible that patients undergoing any nerve-threatening intervention (thyroidectomy, lumbar laminectomy, axillary dissection, radiation) would use such agents and may benefit from them. What about the patients newly diagnosed with diabetes—might there be a role for these agents in the prevention of diabetic neuropathy or prevention of progression or reversal of already established autonomic neuropathy? Will the pharmacologic management of patients with spinal cord injury or neurodegenerative diseases be forever altered?

In the population with prostate cancer, the use of these agents will be predicated not alone on their efficacy in animals and humans but also their safety profile, especially their impact on prostate cancer progression or recurrence. Fortunately, data already exist addressing this, demonstrating the failure of GPI-1046 to promote prostate cancer cell growth in vitro [10], whereas other data suggest that FK506 has no proliferative effect on breast cancer and liver cancer cell lines.

In the final analysis, it will take another 2–3 yr to determine whether these agents are beneficial to men after radical prostatectomy. However, if the data demonstrate improved recovery of erectile function or reduction in time to erectile function recovery or reduction in penile length loss or any combination of these, the agents will be used and given that there is already regulatory agency approval for FK506, if its manufacturer is motivated, it will likely lead the way.

References