Dexmedetomidine, an α2-adrenergic receptor agonist, is used as an anti-anxiety medication. It also exerts a cholinergic effect, thereby reducing the release of TNF-α. We examined our patients who underwent living donor liver transplantation. A trend toward the improvement of hepatocyte injury along with better liver function was observed in the dexmedetomidine-treated group during the first postoperative week. Subsequently, we generated a series of mouse models to investigate the effect of dexmedetomidine on sedation-based tolerance post-transplantation. Indeed, dexmedetomidine inhibited the proliferation of T cells and TNF-α production in a dose-dependent manner. We used dexmedetomidine to treat skin-transplanted mice and observed a significantly prolonged graft survival in mice that were administered a higher dose of dexmedetomidine. These results revealed that dexmedetomidine exerts a dual effect of sedation and immunosuppression. This light-sedation approach will not only make patients calmer in the intensive care unit but also protect allografts from injury. The link between sedation and immunity may be designed toward therapeutic manipulation of the immune response.