Ling Zhi-8 (LZ-8) is a protein from the mycelial extracts of *Ganoderma lucidum* and has immunomodulatory capacities.\(^1\) Formerly it was reported to be mitogenic toward mouse splenocytes and suppressive in vivo by reducing HBsAg-specific antibody production\(^2\) and by preventing the incidence of diabetes in NOD mice.\(^3\) To specify possible clinical use of LZ-8, the mitogenic effects of LZ-8 were tested in the presence of human mononuclear cells (MNC) and T lymphocytes, as well as suppressive capacities of LZ-8 in vitro in an MLC with MNC or T lymphocytes and Epstein-Barr Virus-transformed (EBV) B cells. The immunosuppressive effects of LZ-8 were also investigated in a model of allogeneic mouse skin transplantation and in a model of allografted rat pancreatic islets.

**MATERIALS AND METHODS**

**Mitogenic Activity of LZ-8**

Human MNC or purified T cells were incubated with 3 LZ-8 concentrations (0.1, 1, and 10 \(\mu\)g/mL) for 3, 4, 5, 6, and 7 days.

**Immunosuppressive Activity of LZ-8 In Vitro**

Human T cells were incubated with irradiated allogeneic EBV-B cells and LZ-8 in three concentrations (0.1, 1, and 10 \(\mu\)g/mL) for 6 days.

**Mouse Skin Transplantation**

B10.D2 mice \((H-2^d)\) served as skin donors and C57Bl10 mice \((H-2^b)\) as recipients. Full-thickness skin flaps were attached to the flank of recipients after removal of a corresponding skin area. Rejection occurred on the day of complete necrosis of the transplanted skin. Group 1 (controls, \(n = 12\)) received an injection of saline, twice per week; group 2 (\(n = 11\)) received 15 mg/kg LZ-8, twice per week; and group 3 (\(n = 12\)) received 7.5 mg/kg LZ-8 four times per week.

**Rat Pancreatic Islet Transplantation**

Lewis rats \((RT-1^L)\) were the donors of pancreatic islets and diabetic (streptozotocin IV) F344 rats \((RT-1^F)\) were the recipients of two donor islet grafts. Pancreatic islets were obtained after intraductal distension with collagenase, stationary digestion, filtration, and density gradient centrifugation, as published earlier.\(^4\) Rejection occurred on the day of complete necrosis of the transplanted skin. Group A (controls) rejected their islet grafts after 4.7 ± 0.15 days. MST ± SD of transplanted islets in group B was 9.7 ± 0.8 days and in groups C and D 11.0 ± 0.7 days and 12.5 ± 1.2 days, respectively (groups B, C, D vs A: \(P < .01\); and B vs D: \(P < .05\)).

**DISCUSSION**

LZ-8 proves to have paradoxical immunomodulating effects. In the presence of monocytes, a strong mitogenic response on human MNC by LZ-8 was observed. Evident...
immunosuppression by LZ-8 was demonstrated on the proliferative response of T cells with EBV-B cells in the absence of monocytes. Also, in both tested in vivo allogeneic transplantation models, significant improvement of MST was achieved by LZ-8 in comparison with controls. No toxic side effects of LZ-8 could be discerned in these studies. Future studies should address exact modes of action of LZ-8.

REFERENCES