

drug is concentrated in the central nervous system at theoretically efficacious levels, and the intranasal route holds promise for outpatient studies. These data argue for expanded testing of peptide T in AIDS and other HIV infected, less immunologically suppressed, neuropsychiatrically impaired persons, which is now underway.

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RAPAMYCIN FOR IMMUNOSUPPRESSION IN ORGAN ALLOGRAFTING

SIR,—Rejection and infective complications of immunosuppressive treatment are the main causes of failure in organ allografting in man. To minimise the individual side-effects, azathioprine, corticosteroids, and cyclosporin are combined in small doses. Cyclosporin is the most powerful agent of the three, but can be nephrotoxic. No other immunosuppressants are useful clinically because of toxicity and/or lack of efficacy.

The fungal product, FK506, is immunosuppressive in animals with organ grafts.¹ We confirmed the immunosuppressive effect but animal toxicity was too severe to proceed to clinical trial,² although such a study is now underway in the USA. A compound with structural similarities to FK506, rapamycin, was investigated on the basis of a report that it inhibited experimental allergic encephalitis, adjuvant arthritis, and the formation of humoral antibody in rats.³ Rapamycin is a lipophilic macrolide produced by *Streptomyces hygroscopicus* with both antifungal and antitumour properties.⁴

After intramuscular administration, rapamycin was immunosuppressive in rats given heterotopic heart allografts (table). Graft survival, assessed by palpation of the beating heart, was prolonged in all animals given rapamycin beyond the control period of 7.4 days. Toxicity in the rat was mild: weight loss of less than 10% was observed in the group treated with the highest dose. Non-immunosuppressed nephrectomised pigs with major histocompatibility complex incompatible⁵ renal allografts die from uraemia due to rejection within a mean survival time of 15.1 days.⁶ Survival times of treated pigs (mean 76 days, median 55) and causes of death are shown in the table, with current creatinine values of surviving animals. Three animals survived with normal serum creatinine levels, after not receiving any drug for 6 months. One kidney was rejected early, on day 4. The interstitial pneumonitis in five pigs was probably due to over-immunosuppression. There was no histological or biochemical evidence of rejection in four of these animals and a mild degree of cellular reaction in the fifth, which had had its immunosuppression stopped. Dogs had vomiting and diarrhoea associated with ulceration of the mouth and thrombocytopenia after daily oral doses of 0.25-5 mg/kg. At necropsy all the dogs had gastrointestinal ulcers from the mouth to the colon, secondary to acute necrotising fibrinoid vasculitis of arterioles and small arteries. The lesions were present even in dogs treated with an apparently non-immunosuppressive regimen of 2 mg/kg on days 3-5 (table).

SURVIVAL OF ALLOGRAFTS

Species and organ	Dose (mg/kg)	Survival	
		Days	Mean (SE) survival
<i>Rat heart</i> [†]			
n = 4	50 × 10 days	> 100	100
n = 4	10 × 10 days	66,77,88, > 100	82 (7)
n = 4	2 × 10 days	58,59,59,66	60 (2)
n = 4	1 × 10 days	34,49,52,55	47 (5)
n = 4	0.5 × 10 days	19,20,20,35	23 (4)
n = 5	10 on days 3-6	15,18,18,19,21	18 (1)
n = 10	0	7-8	7.4 (0.2)
<i>Pig kidney (n = 9)</i> [‡]	2 × 64 days	4*,48†,49†,50†,55†,63†, > 251, > 266, > 274	76 (17)§
<i>Dog kidney (n = 7)</i> [¶]	2 on days 3-5	9†,10*,14*, 14*, 15*, 16*, 23*	14 (2)¶¶

Major pathological findings: * = rejection; † = interstitial pneumonitis but no vasculitis; and ‡ = toxicity. Latest creatinine (µmol/l): §140, 161, 235, 176, 239, 283, 220, 137, and 148; ¶294, 503, 1758, 1708, 1388, 871, and 541.

Like FK506, rapamycin is a powerful immunosuppressant that is especially toxic in dogs. The vasculitic lesions, however, were largely confined to the gastrointestinal tract with rapamycin, whereas with FK506 vasculitis was widespread, including in the heart.² If rapamycin, which appears to have little toxicity in primates (Dr J. Chang, Wyeth-Ayerst), is found to have a satisfactory therapeutic index and is effective as an immunosuppressant in primates with organ allografts, then the compound has potential clinical use. Vasculitis in the dog remains a worry and raises the question of a species idiosyncratic reaction.

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LEWIS NEGATIVE GENOTYPE AND BREAST CANCER RISK

SIR,—Mr Phipps and Mr Perry's data (May 27, p 1198) support an association between the Lewis negative genotype and breast cancer, but their findings have been challenged by Prof Petrakis et al (July 1, p 41). There are difficulties in the genetic interpretation of Lewis phenotypes, and they preclude the use of this system in paternity and forensic studies. Lewis antigens are adsorbed onto the red cell surface from the plasma and the Le(a-b+) phenotype can only arise by interaction between the products of Le, Se, and H genes. Since only one Le gene exists Phipps and Perry's hypothesis is that the Lewis negative genotype is due to a chromosomal deletion should mean that the observed increase in the Le(a-b-) phenotype would be equally shared from the Le(a+b-) and Le(a-b+) pool of patients. Saliva studies, which are the most reliable way to Lewis type patients as long as one is aware that Le(a-b+) people will secrete Le^a as well as Le^b substance, show the increase in the Le(a-b-) phenotype to be solely at the expense