Supplementary Table 2: Side effects of common immunosuppressant drugs

		human	NHP	mouse	rat	dog	pig	sheep
Glucocorticoids (GCs)	Dexamethasone® (DM) Prednisolone® (P)	skin atrophy disturbed wound healing osteoporosis muscle atrophy/myopathy cataract, glaucoma diabetes mellitus adrenal insufficiency "steroid psychosis" (at >40 mg P×d^{-1} for 2 weeks) hypertension dyslipidemia reduced fibrinolysis peptic ulcers gastrointestinal bleeding pancreatitis oral candidiasis infections[1]	n.s.i.	10% mortality after 21 days at a single dose of 87.5 mg×kg^{-1} infections[2] osteoporosis[3]	hypertension (at 3 mg DM×kg^{-1}×d^{-1})[4]	hypertension (at 0.5 mg DM×kg^{-1}×d^{-1})[4]	polydipsia / -uria reversible rectal eversion weight loss lymphocytopenia decreased albumin levels weight loss in thymus and lymph nodes neutrophilia (at 2-6 mg DM×kg^{-1}×5×weekly for 5 weeks)[5]	hypertension after prenatal treatment with BM[6] fetal growth retardation after maternal administration of BM[7]
Cytostatic drugs	Azathioprine (Az)	myelosuppression: anaemia, red blood cell aplasia, thrombocytopenia, pancytopenia carcinogenic mutagenic hypersensitive reactions interstitial pneumonitis gastrointestinal reactions[8]	n.s.i.	anemia moribund splenic T-cell lymphomas weight loss[9]	hepatotoxicity decreased blood cell counts[10]	cytopenia hepatotoxicity[11] myelotoxicity[12]	hepatotoxicity[13]	n.s.i.
	Cyclophosphamide® (CY)	<u>common:</u> mutagenic carcinotoxic teratogenotoxic[14] leucopenia (reversible) bone marrow suppression alopecia nausea and vomiting (>50 mg CY×kg^{-1}, 65-70% of patients) hemorrhagic myocardial necrosis (50 mg CY×kg^{1}) <u>rare:</u> pneumonitis fibrosis chest deformity[15]	rhesus monkey: hematopoetic recovery after 200 mg×kg^{-1} cardiac toxicity[16] cynomolgus monkey: anemia[17]	alopecia[18] teratogen[19] mutagenic[20]	mutagenic at 0.62 mg×kg^{-1} [20] loss and malformation of offspring after pre- and postimplantation exposure[21] cardiotoxic[22] teratogenic[23]	lethal at 100 mg×kg^{-1} reversible pancytopenia gastronintestinal toxicity[16]	oral and gastrointestinal toxicity: oral mucositis, ulcers in the soft palate bone marrow aplasia (at 60 mg×kg^{-1} for 2 days) lower spleen and intestinal weights dehydratation sepsis pneumonia decreased blood iron levels[24] emesis[25]	in an asbestosis model: impaired lung function decreased survival increased susceptibility to bacterial pneumonia enhanced fibrotic process in the lung[26]
	Methotrexate® (MTX)	<u>common:</u> minor myelotoxicity nephrotoxicity mucositis (20% of patients), nausea and vomiting <u>rare:</u> ocular irritation erythema and desquamation pleuritis reversible oligospermia[27]	cynomolgus monkey: diarrhea vomiting anemia leucopenia thrombocytopenia[28]	at 260 mg×kg^{-1}: decreased appetite and activity hair loss diarrhea purulent, bloody stool chills weight loss intestinal mucositis 66.7% mortality leucopenia[29]	arthritis nose bleeding diarrhea rapid body weight loss at 1.5 mg×kg^{-1} every second day[30]	delayed emesis[31] gastrointestinal irritation ulcerative fibronecrotic enteritis bloody diarrhea hepatotoxicity[32]	diarrhea vomiting violent muscle fasciculation[33]	negligible adverse effects after i.a. administration[34]
	Mycophenolate mofetil® (MMF)	gastrointestinal intolerance not associated with erosion[35]	mutagenic[35]	none at 40 mg×kg^{-1}×d^{-1} [36]	none at 40 mg×kg^{-1}×d^{-1} [36]	slight elevation of alkaline phosphatase level at 20 mg×kg^{-1}×d^{-1} gastrointestinal symptoms at 40 mg×kg^{-1} (dose related): gastritis diarrhea anorexia	combination therapy (Tcr, P, MMF): gastric rupture pneumonia septic arthritis toe abscess diarrhea decreased weight gain[37]	n.s.i.
Immunophillin drugs	Ciclosporine A® (CsA)	multiorgan toxicity (at 1 and 5 mg×kg^{-1}×d^{-1} p.o.) infections hepatotoxicity interstitial pneumonia[38] hypertension hypercholesterolaemia nephrotoxicity neurotoxicity disturbances in glucose metabolism hirsutism gum hyperplasia gingivitis bilirubinaemia gastrointestinal heamorrhage cholestatic jaundice hypomagnesaemia thrombosis gastritis[39]	cynomolgus monkey: at 150 mg CsA×kg^{-1}×d^{-1} p.o.: pneumonia 15% diarrhea[40]	hepatotoxicity[41] at 30 mg CsA×kg^{-1}×d^{-1}: pancreatic islet injury[42] nephrotoxicity[43]	at 20 mg CsA×kg^{-1}: hypotension (unaltered at 10 mg CsA×kg^{-1})[44] at 25-50 mg CsA×kg^{-1}: renal dysfunction (decreased renal inulin clearance, reduced filtation)[45] nephrotoxicity[46]	<u>common (at 5 mg CsA×kg^{-1}×d^{-1}):</u> 25% of the dogs showed vomiting 15% showed diarrhea/soft stool <u>rare:</u> decreased appetite/anorexia infections lethargy nodules/cycsts papillomatosis gingival hyperplasia lymphadenopathy reproductive disorders neurological disorders[47]	infections (pneumonia, septic arthritis) at 40 mg×kg^{-1}×d^{-1} [48]	no toxicity on organ or skin grafts (blood levels: 3 000-8 000 ng×mL^{-1}) reversible increased bilirubin level decreased albumin level renal tubulus necrosis[49] at 12 mg×kg^{-1}×d^{-1} for 5 days (blood levels: 1 532-2 133 ng×mL^{-1}): hypertension increased heart rate nephrotoxicity anuria slight reduction of potassium level[50]
	Tacrolimus® (Tcr)	hypertension alopecia pruritus diarrhea disturbances in glucose metabolism neurotoxicity tremor hypomagnesaemia thrombosis gastritis hirsutism gum hyperplasia gingivitis bilirubinaemia gastrointestinal heamorrhage cholestatic jaundice[39] nephrotoxicity[51]	baboon: at 0.3 mg Tcr×kg^{-1}×d^{-1}: heart/gastrointestinal toxiciy (necrosis, arteritis, micromyocardial infarction)[52]	nephrotoxicity[53]	at 4 mg Tcr×kg^{-1}×d^{-1} p.o.: inhibition of weight gain[54] nephrotoxicity neurotoxicity[55]	at 0.2-5 mg Tcr×kg^{-1}×d^{-1}: heart/gastrointestinal toxiciy (necrosis, arteritis, micromyocardial infarction) hepatotoxicity acinar cell degeneration in pancreas[52]	nephrotoxicity[51] at 0.3 mg×kg^{-1}×d^{-1}: heart failure (necrosis smooth mucle cells in the coronary arteries, neutrophilic infiltrate in the myocardium) pulmonary oedema cyanosis tachypnea no nephrotoxicity[56]	n.s.i.
	Rapamycin® (Rpm)	pulmonary toxicity anemia leukopenia thrombocytopenia hyperlipidemia posttransplantation diabetes hypophosphatemia lymphedema hypertension acne, follicilitis stomatitis and mucous membrane disorders edema nail and hair pathologies gonadal complications surgical wound complication infections gastrointestinal complication[57]	cynomolgus monkey: weight loss diarrhea lymphopenia neutrophilia no histologic abnormities[58]	diabetes[59] elevated BUN levels decreased body weight low nephrotoxicity (intracytoplasmic vacuolization in proximal tubules)[60]	sexual hormone dysfunction seminiferous tubule dystrophy reversible spermatogenesis blockade[61] at 2 mg×kg^{-1}×d^{-1}: decreased food intake and concomitant weight loss glucose intolerance hyperinsulinaemic hyperglycaemic[62]	pancreatitis biliary duct occlusion[63] from a dose of 0.3 mg Rpm×kg^{-1}×$week^{-1}$: anorexia diarrhea bloody stool decreased body weight (44% in 3 weeks) increased serum amylase levels mucosal necrosis and fibrinoid necrosis in the intestinal tract vasculitis in heart, lung and spleen[64]	at 0.25-0.75 mg×kg^{-1}×d^{-1}: no gastrointestinal side effects central congestions and ischemic necrosis in liver pneumonia decreased weight gain[65]	n.s.i.
Cell therapy	Regulatory T cells (T_{regs})	possibility that Tregs convert into IL-17-producing proinflammatory cells on-target toxicity on-target hepatotoxicity cytokine release syndrome multi organ failure central nervous system toxicity lethal off-target toxicity by TCR cross-reactivity[66] tumor induction[67]	n.s.i.	no toxicity observed in xenogeneic GvHD model[68] lethal graft versus host disease-like phenotype by TCR mispairing[69] tumor induction[67]	n.s.i.	cytotoxicity reversible skin erythema reversible alterations in liver function: AST >600 U×L^{-1} AP >700 U×L^{-1} increased bilirubin level[70]	n.s.i.	n.s.i.
	Mesenchymal stem cells (MSCs)	n.s.i.	n.s.i.	see rat	clotting of pulmonary/ cerebral vessels after intravenous/intracarotid injection[71]	potential pulmonary complications after intravenous delivery[71]	n.s.i.	n.s.i.
Antibodies	Anti-lymphocyte globulin® (ALG)	<u>common:</u> fever chills leucopenia thrombozytopenia dematologic manifestations (rashes, urticaria, pruritus, wheal, flare) <u>rare (<5% patients):</u> cardiovascular reactions (myocarditis, "cardiac irregularity", chest pain, hyper- and hypotension, tachy- and bradycardia)[72]	cynomolgus monkeys: no detectable acute or chronic toxic effects[73]	bone marrow toxicity: 50% decrease in colony-forming unit 24 hr after 1 mL i.v. ALG[74]	lymphopenia[75] nephritis[76]	n.s.i.	n.s.i.	n.s.i.
	Anti-thymocyte globulin® (ATG)	increased incidence of fever hematologic abnormalities cytomegalovirus infections increased incidence of posttransplant lymphoproliferative disease[77] infectious complications increased risk of malignancy after organ transplantation decreased lymphocyte, erythrocyte, platelet and reticulocyte count[78]	marked depletion of paracortical lymphocytes in spleen and mesenteric lymph nodes moderate thrombocytopenia decrease in peripheral lymphocyte count[79]	n.s.i.	n.s.i.	leucopenia lymphopenia thrombocytopenia increased serum alanine aminotransferase activity no histologic changes[80]	n.s.i.	n.s.i.
	Rituximab® (RTB)	acute allergic reactions infusion reactions (in >25% of patients) tumor lysis syndrome mucocutaneous reactions progressive multifocal leukoencephalopathy neutropenia slow recovery of B cells infections reactivation of hepatitis intestinal perforation interstitial pneumonia[81]	cynomolgus monkey: no adverse effects at 16.8 mg×kg^{-1} [82] at single dose of 100 mg×kg^{-1} and multiple dose of 20 mg×kg^{-1}×$week^{-1}$: B cell depletion lymphoid atrophy[81]	n.s.i.	none at 375 mg per m^2 [83]	n.s.i.	n.s.i.	n.s.i.
	CAMPATH H-1H® (CHH)	cytopenia infusion reactions (cytokine release syndrome) infections (bacterial, viral, fungal, protozoan infections reactivation of latent cytomegalovirus and herpes zoster infections[81]	cynomolgus monkey: at 1 mg×kg^{-1}: reversible lymphopenia neutropenia hypotension fever immunogenic effects[81]	in human-CD52 transgenic mice: transient increase in serum cytokines depletion of peripheral blood lymphocytes[81]	n.s.i.	n.s.i.	n.s.i.	n.s.i.

AP = alkaline phosphatase, AST = aspartate aminotransferase, BM = betamethasone, BUN = blood urea nitrogen, DM = dexamethasone, IL-2 = interleukin 2, n.s.i. = no standardized information availabale, TCR = T cell receptor,

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