

## Report from the ASGT Ad Hoc Committee on Retroviral-mediated Gene Transfer to Hematopoietic Stem Cells

**Table 1: Published Retroviral Gene Transfer Studies in Non-Human Primates**

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Kantoff <i>et al.</i> , 1987)	Rhesus	4	BM MNCs	3 < 1 yr, 1 14 years	RV	Neo, ADA	None long-term	None
(Bodine <i>et al.</i> , 1990)	Rhesus	3	BM MNCs	1 year	RV (helper-contaminated)	Neo	< 1%	None
(Donahue <i>et al.</i> , 1992; Vanin <i>et al.</i> , 1994)	Rhesus	10	BM MNCs or CD34+ cells	6 animals not developing lymphoma followed 120 months (0.5-1% marking)	RV (helper-contaminated)	Neo	0-10%	3 T cell lymphomas (months 3-4)
(Van Beusechem <i>et al.</i> , 1992)	Rhesus	3	BM MNCs	< 1 yr	RV	ADA	< 1%	None
(Bodine <i>et al.</i> , 1993)	Rhesus	2	CD34+ BM, ablative TBI	96 months	RV	ADA	1%	None
(Van Beusechem <i>et al.</i> , 1993)	Rhesus	3	BM MNCs	13 months	RV	ADA	< 1%	None
van Besc 1994(Van Beusechem <i>et al.</i> , 1994)	Rhesus	2	CD34+, 11b-BM, ablative TBI	15 months	RV	ADA	< 1%	None

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Van Beusechem <i>et al.</i> , 1995)	Rhesus		CD34+ BM, ablative TBI		RV	ADA	< 1%	
(Xu <i>et al.</i> , 1995)	Rhesus	3	CD34+ BM, ablative TBI	96 months	RV	gluco-cerebrosidase	< 1%	None
(Dunbar <i>et al.</i> , 1996)	Rhesus	4	CD34+ BM or PBSC	12 months	RV	Neo	1%	None
(Donahue <i>et al.</i> , 1996)	Rhesus	3	CD34+/Thy1+ BM, ablative TBI	12 months	RV	gluco-cerebrosidase	< 1%	None
(Kaptein <i>et al.</i> , 1997)	Rhesus	2	BM, ablative TBI	36 months	RV	ADA	<1%	None
(Kiem <i>et al.</i> , 1997)	Baboon	4	CD34+ BM	6 months	RV	Neo	1%	None
(Bunnell <i>et al.</i> , 1997)	Rhesus	3	T cells	6 months	RV	Neo	Transient 10%, then < 0.1%	None
(Kiem <i>et al.</i> , 1998)	Baboon	5	CD34+ BM	up to 67 months	RV	Neo, AlkP	1-10%	None
(Tisdale <i>et al.</i> , 1998)	Rhesus	8	CD34+ PBSC, ablative TBI	3-60 months	RV	Neo	1-3% in 4 animals	None
(Donahue <i>et al.</i> , 1998)	Rhesus	3	T cells	6 months	RV	antisense tat/rev, Neo	0.2-2%	None
(Ierino <i>et al.</i> , 1999)	Baboon	5	BM MNCs	< 6 months	RV	swine MHC gene, Neo	< 1%	None

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Rosenzweig <i>et al.</i> , 1999)	Rhesus	6	CD34+ BM non-ablative TBI	12 months	RV	GFP	< 1%	1 animal with hemolytic anemia 20 wks post-transplant, responded to steroids, no increase in vector-containing cells
(Bunnell <i>et al.</i> , 1999)	Rhesus	5	CD34+ PBSC, or BM ablative TBI	12 months	RV	Neo	<1%	None
(Hanazono <i>et al.</i> , 1999)	Rhesus	4	T cells	12 months	RV	Neo and non-expressed Neo	< 1%	None
(Huhn <i>et al.</i> , 1999)	Rhesus	4	CD34+ PBSC	50-150 months	RV	Neo	1-2%	None
(An <i>et al.</i> , 2000)	Rhesus	4	CD34+ PBSC or BM, ablative TBI	56-60 months	LV	GFP	0.1-2%	None
(Andrews <i>et al.</i> , 2000)	Baboon	3	CD34+ or CD34- BM, allo cells	15 months	RV	Neo	< 1%	None
(Heim <i>et al.</i> , 2000)	Rhesus	10	T cells or CD34+ PBSC/ablative TBI	6-50 months	RV	Neo and non-expressed Neo	0.1-3%	None
(Wu <i>et al.</i> , 2000; Kim <i>et al.</i> , 2000; Schmidt <i>et al.</i> , 2002)	Rhesus	4	CD34+ PBSC/ablative TBI	40-60 months	RV	Neo	1-15%	None

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Donahue <i>et al.</i> , 2000)	Rhesus	5	CD34+ PBSC/ablative TBI	6-60 months	RV	GFP	3-5%	None
(Shi <i>et al.</i> , 2001)	Rhesus	3	CD34+ PBSC/ablative TBI		RV	Neo, G6PD	1-3%	None
(Sellers <i>et al.</i> , 2001)	Rhesus	2	CD34+ PBSC/ablative TBI	48 months	RV	Neo, MDR1	1-5%	None
(Kurre <i>et al.</i> , 2001)	Baboon	7	CD34+ BM	up to 3 years	RV	Neo, GFP	1-8%	None
(An <i>et al.</i> , 2001)	Rhesus	6	CD34+ PBSCs	40-44 months (GFP), 18-20 months (IL2RG)	LV	GFP (n=4) or human IL2RG (n=2)	0.5-5%	None
(Rosenzweig <i>et al.</i> , 2001)	Rhesus	4	CD34+ PBSC/non-ablative TBI	16-20 months	RV	CD24	up to 35% first 2-4 months, then < 1%	None
(Hanazono <i>et al.</i> , 2002b)	Cyno.	3	CD34+ BM	12-24 months	RV	GFP	< 1%	None
(Takatoku <i>et al.</i> , 2001)	Baboon	4	CD34+ PBSC/ablative TBI	36-42 months	RV	Neo	1-25%	None

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Kelly <i>et al.</i> , 2002)	Rhesus	6	CD34+ PBSC/ablative TBI	up to 40 months	RV	GFP	<1%-5%, one animal with oligoclonal marking only, up to 80% marking for 6 months, now only 1%	None
(Hanazono <i>et al.</i> , 2002a)	Rhesus	8	CD34+ BM	< 12 months	RV	GFP, non-expression neo, truncated G-CSFR/estrogen R chimera	0.5-1% with estrogen agonist treatment, 14 clones identified by inverse PCR	None
(Kluge <i>et al.</i> , 2002)	Rhesus	3	CD34+ PBSC/ablative TBI	20-30 months	RV	Neo	0.1-5%	None
(Kurre <i>et al.</i> , 2002)	Baboon	4	CD34+ BM	20 months	RV	GFP/YFP	2-6%	None
(Horn <i>et al.</i> , 2002a)	Baboon	4	CD34+ BM	30 months (1 animal), rest < 6 months	LV/RV	GFP/YFP	10% (all from LV, slow increase between 3-10 months)	None
(Kiem <i>et al.</i> , 2002)	Baboon	6	CD34+ BM	< 12 months	RV	GFP	<2%	None
(Horn <i>et al.</i> , 2002b)	Baboon	3	CD34+ BM	12 months	RV	GFP/YFP	10-30%	None

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Hematti <i>et al.</i> , 2003)	Rhesus	5	CD34+ PBSC or BM/ablative TBI		RV	Neo	None	None

**Table 2: Published Retroviral Gene Transfer Studies In Dogs*****A. Autologous Transplantation of Transduced Bone Marrow or Peripheral Blood Cells***

Reference	Number	Method or Cellular Target	Follow-up in publication	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Carter <i>et al.</i> , 1992)	9	21-day cultured marrow, ablative TBI	21 months	RV	Neo	< 1%	None
(Bienzle <i>et al.</i> , 1994)	18	21-day cultured marrow, no ablation before infusion	24 months	RV	Neo	CFU up to 20% ? PB < 1%	None
(Lutzko <i>et al.</i> , 1999a)	5	21-day cultured marrow, no ablation	36 months	RV	canine alpha-L-iduronidase	< 1%	None
Kiem	2	PBSC, MHCII+, 11 day culture, ablation	17 months	RV	Neo	< 1%	None
(Barquinero <i>et al.</i> , 1995)	19	Bone marrow or PBSC, no ablation (4), some ablation (12), complete ablation (3)	< 1 year	RV	Neo	< 1%	None
(Schuening <i>et al.</i> , 1991) Kiem 1996	5	Bone marrow, ablative TBI	63 months (1), 50 months (1), 24 months (3)	RV	Neo, ADA	<1%	None
(Kiem <i>et al.</i> , 1999)	4	CD34+ BM, ablative TBI	18 months	RV	Neo	Up to 10%	None

Reference	Number	Method or Cellular Target	Follow-up in publication	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Goerner <i>et al.</i> , 1999)	4	CD34+ BM, ablative TBI	< 1 year	RV	Neo	Up to 10-15%	None
(Goerner <i>et al.</i> , 2001)	3	CD34+ BM, ablative TBI	23 months	RV	GFP, Neo	Up to 10%	None
(Georges <i>et al.</i> , 2001)	8	Donor T cells, allo transplant	< 1 year	RV	GFP, Neo	Up to 7%	None
(Bruno <i>et al.</i> , 2001)	3	CD34+ BM, ablative TBI	12 months	RV	Neo	< 1%	None
{Neff, Horn, et al. 2002 4724 /id}	1	CD34+ BM, ablative TBI	6 months	RV	MGMT p140K mutant	pre-drug 15-20%, post-O6PG and BCNU 55-80%	None
(Neff <i>et al.</i> , 2002)	2	CD34+ BM, ablative TBI	12 months	RV	conditional mpl with dimerization domain	1-2%, transient increases to 10% with dimerizer rx	None, except plt decrease on dimerizer
(Whitwam <i>et al.</i> , 1998),(Licht <i>et al.</i> , 2002)	8	Bone marrow, 200 rads TBI one dog taxol 23 months	16 months, 3 dogs 23 months, one dog 33 months	RV	IL2Rgamma, Neo, MDR1	up to 25% but transient	None
(Ting <i>et al.</i> , 2002)	3	Bone marrow, no ablation	< 6 months	RV	IL2RG	10-20% short-term	died of SCID

***B. Direct Injection of Vector or Transduced Cells Into Pre-Immune Fetuses or Neonates***

<b>Reference</b>	<b>Number</b>	<b>Method</b>	<b>Follow-up</b>	<b>Vector</b>	<b>Trangene (s)</b>	<b>Stable Gene Transfer Levels</b>	<b>Reported AEs</b>
(Omori <i>et al.</i> , 1999)	6	Injection of transduced human BM	< 12 months	RV	Neo	< 1% then none	None
(Lutzko <i>et al.</i> , 1999b)	12	Vector Injection	< 12 months	RV	Canine alpha-L-iduronidase or Neo	< 1%	None other than disease (MPS I) progression
(Meertens <i>et al.</i> , 2002)	7	Vector Injection	< 12 months	RV	Canine alpha-L-iduronidase	< 1%	None other than disease (MPS I) progression
(Xu <i>et al.</i> , 2002)	5	Vector Injection	6 months	RV	beta-glucuronidase	< 1%	None
(Ponder <i>et al.</i> , 2002)	7	Vector Injection	14-17 months	RV	beta-glucuronidase	< 1%	None

**Table 3: Published Retroviral Gene Transfer Studies in Sheep**

Reference	Species	Number	Method	Follow-up	Vector	Trangene (s)	Stable Gene Transfer Levels	Reported AEs
(Kantoff <i>et al.</i> , 1989)	Sheep	10	transduced human BM cells IP	24 months	RV	Neo	< 1%	None
(Tran <i>et al.</i> , 2001)	Sheep	14	vector IP injection (no human cells)	40 months (9 animals)	RV	B-gal, Neo		None0-6.5%
(Porada <i>et al.</i> , 2002)	sheep	7-primary 4 secondary 4 tertiary	vector IP injection after transplant of human BM cells		RV	Neo, B-gal	10-20%	None
(Tsai <i>et al.</i> , 2002)	sheep	6	transduced human X-SCID CD34+ BM IP		RV	IL2R	All human T cells +	None
(Lucas <i>et al.</i> , 2002)	sheep	4	transduced human CD34+ BM IP	6 months	RV	B-gal	> 10%	None

**Table 4: Published Retroviral Gene Transfer Studies in Other Large Animal Models**

Reference	Species	Number	Method	Follow-up	Vector	Transgene (s)	Stable Gene Transfer Levels	Reported A.E.s
(Lothrop, Jr. <i>et al.</i> , 1991)	Cat	4	BM MNCs	< 1 year	RV	Neo	< 1%	3 animals diabetes day 90
(Nelson <i>et al.</i> , 1997)	Rabbit	5	Direct BM injection of vector	up to 20 months	RV	Neo	< 1%	None
(Josephson, Sabo & Abkowitz, 2000)	Cat	1	BM MNCs	14 months	RV	Neo	< 1%	None
(Sonntag <i>et al.</i> , 2001)	Minature Swine	5	BM MNCs	12 months	RV	MHC class II	< 1%	None

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