

Immune Homeostasis: Regulatory T cell subsets

Treg Subsets

Regulatory T Cell Types	Natural Treg (nTreg)		
	nTreg	$\gamma\delta$ T	NKT
Phenotype	CD4+/CD25 ^{high}	TCR $\gamma\delta$	CD3, NK1.1, CD56
MHC Restriction	No	Yes	CD1d
Cellular proteins	CTLA4, GITR, Foxp3	TCR	TCR
Origin	Thymus	Thymus	Thymus
CD28 dependency	Role in thymic development & maintenance in periphery	Yes	
Mechanism of suppression/Target cells	Contact dependent, Granzyme B-dependent, makes TGF- β /APC & T	Contact, cytokines	Makes, IL-4, IL-10, IFN- γ , TGF- β /tumor cells
In vivo role	Self tolerance, suppresses autoreactive T cells, non-inflammatory, specific for self antigens	Mucosal immunity	Innate immunity
In vitro propagation	Difficult to expand in vitro	TCR	IL-15, Flt3L

Overview

A complex network of regulatory mechanisms exists which mitigates immune-mediated pathology, preventing autoimmune phenomena and controlling peripheral damage during an immune response. Distinct subsets of regulatory T cells function to suppress the outgrowth of potentially pathogenic antigen-reactive T cells, control tolerance, autoimmunity and response to allografts, allergens, and infections. The renaissance in understanding of the role of these regulatory T cells has come about as a dramatic reversal over the last 40 years.

Gershon's laboratory showed in 1970 that adoptive transfer of T cells from tolerized mice could suppress responses in recipient animals. At this time a lack of understanding of the cytokine networks and cell subsets rendered characterization of the suppression phenomenon difficult and invited skepticism. The inability to isolate T cell clones bearing the suppressor phenotype led many immunologists to question whether such suppressor T cells actually existed.

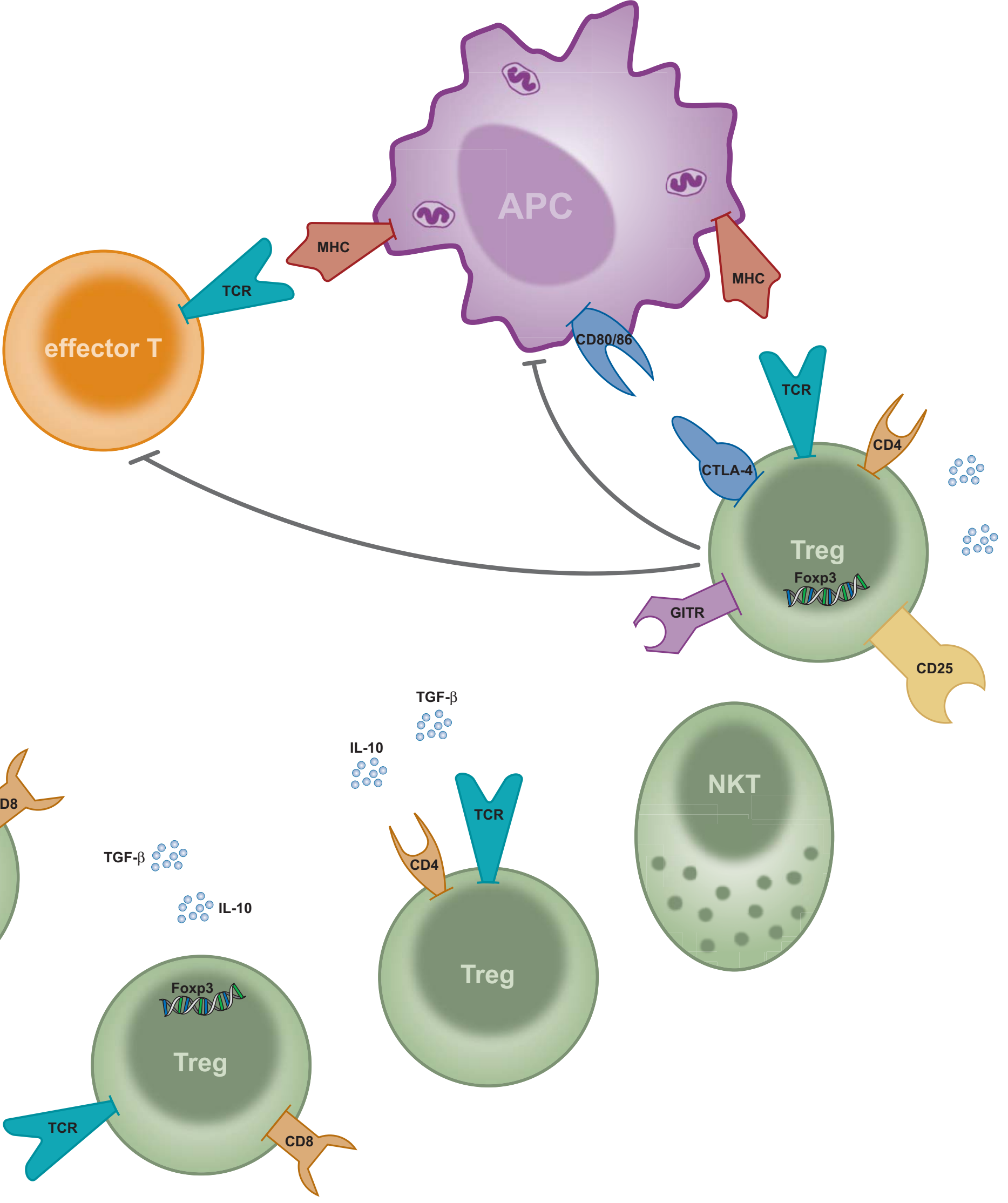
Renaissance of the Suppression - Vivre la Regulation!

Sakaguchi *et al* demonstrated in 1985 that reconstitution of CD4 cells inhibited disease development in a thymectomized, organ-specific autoimmune model. Later, they showed that this suppression was mediated by a small subset of CD4+CD25+ T cells. The identification of the immune suppressive activity within this population was the turning point of the new age of T cell suppressors, now termed regulatory T cells (Treg).

Candidate Treg cell types, based largely on their capacity to produce suppressive cytokines, such as IL-4, IL-10, and TGF- β , include 1) IL-10-producing, antigen-specific Treg1, 2) TGF-beta-secreting Th3, 3) CD8+, 4) NKT, 5) $\gamma\delta$ T and 6) CD4+CD25+ T cells. Two categories of CD4+CD25+ Treg cells have been proposed which differ in origin, antigen specificity and effector mechanism; these have been designated either as naturally occurring, nTreg, or induced, iTreg.

There are still no cell surface molecules that uniquely distinguish functional regulatory cells from conventional T cells, rendering some controversy. The transcription factor Foxp3, initially reported to be expressed uniquely by CD4+CD25+ Tregs, likewise, may not necessarily be an exclusive lineage marker for these cells. Growing evidence for involvement of multiple cell types with regulatory function emphasizes the heterogeneity and redundancy of this necessary homeostatic mechanism. Further studies will undoubtedly introduce increased understanding and appreciation for the complex nature of this reborn field of immunological research.

References:
J. Clin. Invest. 2004. 114:1198-1208. Sem in Immunol. 2005. 16: 81-88. J. Immunol. 2005. 174: 1783-1786. J. Immunol. 2004. 172: 5986-5993. Immunology. 2003. 19: 165-168.



Regulatory T Cell Types	Adaptive or Inducible Tregs (iTreg)				
	Tr1	Th3	CD8	CD8	DN
Phenotype	CD4+/CD25-	CD4+/CD25-	CD8+	CD8+/CD28-	TCR+/CD4-/CD8-
MHC Restriction			Qa-1 (HLA-E)	MHC I	MHC I
Cellular proteins	CD25 ^{low} variable CD45Rb ^{low} Foxp3-	CD25 ^{low} variable CD45Rb ^{low}		Foxp3+	
Origin	Thymus? Thru nTregs?	Thymus? Thru nTregs?	Thymus/ periphery?	Thymus?	Thymus?
CD28 dependency	Not for development or function		Yes	Yes	
Mechanism of suppression/Target cells	Thru cytokines, makes IL-10	Thru cytokines, makes TGF- β	Contact	Thru IL-10, IL-6, IFN- γ , contact	Contact
In vivo role	Inflammatory response to microbes, or transplanted tissues, specific for tissue & foreign antigens			Tumor induced suppression	Alloantigen-specific prevention of GVHD
In vitro propagation	TCR, IL-10, TGF- β , or Vitamin D			TCR signal	MHC I - mismatched cells

Related Antigens

Antigen	References
CCR4	J Exp Med. 2001. 194:847.
CCR5	PLoS Biol. 2004. 2:E198.
CCR6	Blood. 2004 Epub.
CCR7	J Immunol. 2003. 171:5760. Blood. 2004. 104:895. Blood. 2005. 105:750.
CCR8	J Exp Med. 2001. 194:847. Eur J Immunol. 2002. 32:3506. Blood. 2003. 102:4107.
CD103	Gastroenterology. 2002. 123:1516. Eur J Immunol. 2003. 33:2419. Eur J Immunol. 2004. 34:705.
CD122	Eur J Immunol. 2005. 35:383. J Immunother. 2005. 28:120.
CD134/OX40	Clin Exp Immunol. 2004. 136:373. J Immunol. 2004. 172:3580. Crit Rev Immunol. 2004. 24:251.
CD152	Eur J Immunol. 2004. 34:2996. J Exp Med. 2000. 192:295. J Immunol. 2004. 173:2866.
CD154	J Autoimmun. 2004. 23:241. J Clin Invest. 2004. 114:979.
CD27	Blood. 2005. 105:750. Eur J Immunol. 2005. 35:383.
CD28	Eur J Immunol. 2003. 33:626. J Immunol. 2004. 172:2778.
CD38	J Immunol. 2004. 173:3084. Exp Hematol. 2004. 32:622.
CD45RA	Clin Cancer Res. 2003. 9:606. J Neurosci Res. 2003. 74:296.
CD45RB	J Exp Med. 2000. 192:295. Immunology. 2003. 110:304. J Exp Med. 2003. 197:403.
CD45RO	Immunology. 2003. 110:304.
CD62L	Blood. 2004. 104:895. Immunology. 2003. 110:304. Am J Transplant. 2004. 4:65. Blood. 2004. 104:3804.
CD69	Diabetes. 2005. 54:92.
CD95	Blood. 2005. 105:735.
CLA	J Immunol. 2003. 171:5760.
CXCL12	Cancer Res. 2004. 64:8451.
CXCR4	Cancer Res. 2004. 64:8451.
Foxp3	J Immunol. 2005. 175:4180. J Exp Med. 2005. 202:1141. J Exp Med. 2005. 202:445.
GITR/AITR	Nat Immunol. 2002. 3:135. Eur J Immunol. 2003. 33:579. J Immunol. 2003. 171:708.
Granzyme B	Immunology. 2004. 21:589.
HLA-DR	Immunology. 2003. 110:304. J Immunol. 2004. 172:8435.
Neuropilin	Immunology. 2005. 114:410. Eur J Immunol. 2004. 34:623.
Notch family	J Immunol. 2003. 171:4504. Immunology. 2000. 100:281. Int Arch Allergy Immunol. 1999. 118:122.
PD-1	Curr Opin Immunol. 2002. 14:779.
Perforin	Immunology. 2004. 21:589.
RANK	Curr Opin Immunol. 2002. 14:771. J Immunother. 2002. 25:202.
TGF- β	J Immunol. 2004. 172:834. Cytokine Growth Factor Rev. 2003. 14:85.
TLR family	J Exp Med. 2003. 197:403. J Immunol. 2004. 172:3712.
TRANCE	Curr Opin Immunol. 2002. 14:771. J Immunother. 2002. 25:202.

eBioscience Products

Antibody Format Legend:
 Purified: Black (14-), PE-Cy5.5: Blue (15-), APC-Cy7: Brown (10-)
 FG Purified: Gray (16-), PE-Cy5.5: Pink (35-), Cy5: Light Blue (19-)
 Biotin: Crimson (13-), PE-Cy7: Orange (25-), FG Biotin: Tan (36-)
 FITC: Green (11-), APC: Sage (17-), Alexa Fluor[®]: Magenta
 PE: Red (12-), APC-Cy5.5: Purple (30-), ELISA kit & set, ELISPOT set: Teal (88-)

Specificity	Clone	Formats
AITRL	mAb	Please Inquire
CD3	OKT3	14-0037, 16-0037, 11-0037, 12-0037, Alexa Fluor [®]
	UCHL1	14-0038, 16-0038, 13-0038, 11-0038, 12-0038, 15-0038, 17-0038, 25-0038, 10-0038
	RPA-T4	14-0049, 16-0049, 13-0049, 11-0049, 12-0049, 15-0049, 17-0049, 25-0049, 10-0049
CD4	OKT4	14-0048, 16-0048, 11-0048, 12-0048, 17-0048, Alexa Fluor [®]
	RPA-T8	14-0088, 11-0088, 12-0088, 15-0088, 17-0088, 25-0088, 10-0088
	OKT-8	14-0086, 16-0086, 13-0086, Alexa Fluor [®]
CD8	BC96	14-0259, 13-0259, 11-0259, 12-0259, 17-0259, 25-0259
CD25	BC96	14-0259, 13-0259, 11-0259, 12-0259, 17-0259, 25-0259
CD27	O323	14-0279, 13-0279, 11-0279, 12-0279, 17-0279, 10-0279
	LG.7F9	14-0271, 16-0271, 13-0271, 11-0271, 12-0271, 17-0271
CD28	CD28.2 (costimulatory)	14-0289, 16-0289, 13-0289, 11-0289, 12-0289, 17-0289, 25-0289
	CD28.6 (blockin)	16-0289
CD38	HLT7	14-0389, 11-0389, 12-0389, 15-0389, 17-0389, 25-0389, 30-0389
CD45RA	H1100	14-0458, 13-0458, 11-0458, 12-0458, 15-0458, 17-0458
CD45RO	UCHL1	14-0457, 11-0457, 12-0457, 15-0457, 17-0457
CD45RB	MEM-55	14-7457, 11-7457, 12-7457, 15-7457
CD62L	DREG-56	15-0629, 11-0629, 12-0629, 15-0629, 17-0629, 25-0629, 10-0629
CD69	FN50	14-0699, 11-0699, 12-0699, 17-0699, 25-0699
CD103	B-Ly7	14-1038, 11-1038, 12-1038
CD134	ACT375	14-1347, 11-1347, 12-1347, 17-1347
CD152	14D3	14-1529, 16-1529, 13-1529, 12-1529
CXCR4	12G5	14-9999, 16-9999, 13-9999, 12-9999, 15-9999, 17-9999, 25-9999
Foxp3	PCH101	14-4776, 13-4776, 15-4776, 17-4776, 12-4776, 17-4776, Alexa Fluor [®] , 88-8318 (Treg Staining Kit w/ APC Foxp3 FJK-16a, FITC CD4, PE CD25)
	236A/E7	14-7979, 12-7979, 17-7979
	eBio7979	14-7979, 12-7979, 17-7979
Granzyme B	Set	88-8099 (ELISA Set), 88-8399 (ELISPOT Set)
	Gb11	14-8899, 12-8899
HLA-DR	LNS	14-9956, 12-9956, 25-9956
IFN- γ	Set/Kit	88-7315 (ELISA Set), 88-7916 (ELISA Kit), 88-7386 (ELISPOT Set)
	MD-1	14-7317, 16-7317
	NIB42	14-7318, 16-7318
	4S.83	14-7319, 13-7319, 11-7319, 12-7319, 17-7319, 25-7319, Alexa Fluor [®]
IL-4	Set/Kit	88-7046 (ELISA Set), 88-7946 (ELISA Kit), 88-7849 (ELISPOT Set)
	MP4-25D2	14-7046, 16-7046, 13-7046, 11-7046, 12-7046, 17-7046
	8D4-3	14-7049, 12-7049, 17-7049
IL-10	Set/Kit	88-7106 (ELISA Set), 88-7906 (ELISA Kit), 88-7805 (ELISPOT Set)
	JES3-9D7	14-7106, 16-7106, 12-7106, 15-7106, Alexa Fluor [®]
	JES3-12G8	13-7109
PD1/CD279	MIH4	14-9969, 12-9969
	1116	14-9989, 16-9989, 13-9989, 11-9989, 12-9989
Perforin	dG9	14-9994, 11-9994, 12-9994
	eBioBOR21	14-9993
RANK	9A725	60-6618
TGF- β 1	mAb	12-8347
	TRANCE (recombinant)	34-8348 (carrier-free recombinant)
	MIH24	14-6619, 13-6619, 12-6619

Specificity	Clone	Formats
CD1d	1B1	14-0011, 16-0011, 13-0011, 11-0011, 12-0011
CD3	145-2C11	14-0031, 16-0031, 13-0031, 11-0031, 12-0031, 15-0031, 17-0031, 25-0031, 35-0031, 36-0031, Alexa Fluor [®]
	17A2	14-0032, 16-0032, 10-0032
CD4	GK1.5	14-0041, 16-0041, 13-0041, 11-0041, 12-0041, 15-0041, 17-0041, 25-0041, 35-0041, 36-0041, Alexa Fluor [®]
	RM4-5	14-0042, 16-0042, 13-0042, 11-0042, 12-0042, 15-0042, 17-0042, 25-0042, 35-0042, 36-0042
CD8a	53-6.7	14-0081, 16-0081, 13-0081, 11-0081, 12-0081, 15-0081, 17-0081, 25-0081, 35-0081, 36-0081, Alexa Fluor [®]
CD8b	CT-CD8b	14-0082, 16-0082, 13-0082, 11-0082, 12-0082, 15-0082, 17-0082
CD25	PC61.5	14-0251, 16-0251, 13-0251, 11-0251, 12-0251, 15-0251, 17-0251, 25-0251, 10-0251, 36-0251
CD27	LG.7F9	14-0271, 16-0271, 13-0271, 11-0271, 12-0271, 17-0271
CD28	37.51	14-0281, 16-0281, 13-0281, 12-0281, 15-0281, 17-0281, 25-0281
CD38	14-0381	14-0381, 16-0381, 13-0381, 11-0381, 12-0381, 15-0381, 17-0381
CD45RB	C363.16A	14-0455, 13-0455, 11-0455, 12-0455
CD62L	MEL-14	14-0621, 16-0621, 13-0621, 11-0621, 12-0621, 15-0621, 17-0621, 25-0621, 10-0621
CD69	H1.2F3	14-0691, 16-0691, 13-0691, 11-0691, 12-0691, 15-0691, 25-0691
CD103	2E7	14-1031, 16-1031, 13-1031, 11-1031, 12-1031
CD122	TM4b1	14-1222, 16-1222, 13-1222, 11-1222, 12-1222
	5H4	14-1221, 16-1221, 13-1221, 12-1221
CD134	OX-86	14-1341, 16-1341, 13-1341, 12-1341
CD152	9H10	14-1521, 16-1521
	UC10-4B9	14-1522, 16-1522, 13-1522, 12-1522
Foxp3	FJK-16a	14-5773, 13-5773, 15-5773, 17-5775, 12-5775, 17-5775, Alexa Fluor [®] , 88-8118 (Treg Staining Kit w/ APC Foxp3 FJK-16a, FITC CD4, PE CD25)
	NRRF-30	14-7979, 12-7979, 17-7979
	eBio7979	14-7979, 12-7979, 17-7979
	150D/E4	14-4774, Alexa Fluor [®]
GITR	DTA-1	14-5874, 16-5874, 13-5874, 11-5874, 12-5874, 17-5874
Granzyme B	Set	88-8099 (ELISA Set), 88-8399 (ELISPOT Set)
	16G6	14-8822, 13-8822, 11-8822, 12-8822
IFN- γ	Set/Kit	88-7314 (ELISA Set), 88-8314 (high sensitivity ELISA Set), 88-7914 (ELISA Kit), 88-8344 (high sensitivity ELISA Kit), 88-7384 (ELISPOT Set)
	XMG1.2	14-7311, 16-7311, 13-7311, 11-7311, 12-7311, 17-7311, 25-7311, 35-7311, Alexa Fluor [®]
	AN-18	14-7313, 16-7313
	R4-6A2	14-7312, 16-7312, 13-7312, 36-7312
IL-4	Set/Kit	88-7044 (ELISA Set), 88-7944 (ELISA Kit), 88-7844 (ELISPOT Set)
	11B11	14-7041, 16-7041, 12-7041, 17-7041, Alexa Fluor [®]
IL-10	Set/Kit	88-7104 (ELISA Set), 88-7904 (ELISA Kit), 88-7804 (ELISPOT Set)
	JES5-16E3	16-7101, 13-7101, 11-7101, 12-7101, 17-7101, 36-7101, Alexa Fluor [®]
	JES5-2A5	14-7102, 16-7102, 13-7102
MHC class II	M5/114.15.2	14-5321, 16-5321, 13-5321, 11-5321, 12-5321, 15-5321, 17-5321
	14-4-4S	14-5980, 13-5980, 11-5980, 12-5980
OX40/CD252	RM134L	14-5905, 16-5905, 13-5905, 12-5905
PD1/CD279	J43	14-9985, 16-9985, 13-9985, 11-9985, 12-9985
	RMP1-30	14-9981, 16-9981, 13-9981, 11-9981, 12-9981
Perforin	eBioOMAK-D	14-9392, 12-9392
RANK	R12-31	14-6612, 13-6612, 12-6612
TRANCE/cd254	IK22/5	14-5952, 13-5952, 12-5952

Specificity	Clone	Formats
CD27	LG.7F9	14-0271, 16-0271, 13-0271, 11-0271, 12-0271, 17-0271
CD28	J319	14-0280, 16-0280, 11-0280, 12-0280
CD152	WKH203	14-1520, 13-1520, 12-1520
Foxp3	FJK-16a	14-5773, 13-5773, 15-5773, 17-5775, 12-5775, 17-5775, Alexa Fluor [®] , 88-8118 (Treg Staining Kit w/ APC Foxp3 FJK-16a, FITC CD4, PE CD25)
	150D/E4	14-4774, Alexa Fluor [®]
IFN- γ	Set	88-7315 (ELISA Set)
	DB-1	14-7310
	Polyclonal	13-7320
MHC Class II	HIS19	14-0920, 13-0920, 11-0920, 12-0920, 17-0920
OX40L	ATM2	14-1340, 16-1340, 13-1340, 12-1340

November 2005
 Compiled by Nooshen Alavardi & David Selye
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