

# Costimulation and B7 Family

## Overview

T cell activation is a tightly regulated event involving complex receptor-ligand interactions, ultimately leading to downstream signaling events. Optimal activation of naive T cells requires at least two signals, antigen recognition and costimulation. The TCR complex, which recognizes antigenic peptides presented by MHC molecules, is critical in maintaining the specificity of the immune response. Signal two, or costimulation, is an antigen-independent signal required for sustained cell proliferation, effector/memory cell generation and prevention of anergy or apoptosis. Since costimulatory molecules are required for the activation of naive T cells their expression is limited to professional antigen presenting cells (APCs). This ensures that only pathogen-specific T cells are activated and minimizes the chances of acquired immune responses being mounted against self.

Numerous costimulatory molecules have been identified playing a role in the initiation of immune responses by T and B lymphocytes. One of the most well studied costimulatory pathways involves the interaction of B7.1 (CD80) and B7.2 (CD86) with their ligand CD28 on naive T cells. Signals provided through CD28-B7 interactions are essential for initial naive T cell activation leading to increased IL-2 production and IL-2R $\alpha$  (CD25) expression. CD28-B7 interactions can be substituted by NKG2D on naive CD8+ T cells. NKG2D binds to the MHC-related proteins MIC and Rae-1 and induces IL-2 production and proliferation. In other cell types, such as B cells, activation requires CD40-CD40L interactions for proper antibody response. CD40L on activated CD4+ T cells binds to CD40 on B cells promoting survival, cytokine receptor expression, and inducing antibody class switch. In addition to the costimulatory pathways that are important in naive lymphocyte activation, other costimulatory molecules play a role in effector/memory lymphocyte activation.

The costimulatory receptors ICOS, OX-40, 4-1BB, and CD27 bind to their ligands B7h, OX-40L, 4-1BL, and CD70, respectively. These interactions enhance the activation, survival, and cytokine secretion of effector/memory, but not naive T and B cells. ICOS affects all aspects of acquired immune responses while CD27 affects only T cell responses. OX-40 and 4-1BB are thought to be more specific, with OX-40 generally affecting CD4+ T cells and 4-1BB usually affecting CD8+ T cells. The pattern of expression of these costimulatory receptors and their ligands differs from CD28-B7 in that they are not constitutively expressed but are induced on differentiated T cells, and their ligands are not restricted to APCs.

T cell activation generally incorporates a self-limiting mechanism, such as inhibitory costimulators, to regulate T cell tolerance and attenuate the immune response. The expanding set of inhibitory costimulators currently includes CTLA-4 (CD152), PD-1, and BTLA. While expression of these molecules is induced following T cell activation, they are absent on naive T cells. CTLA-4 binds the same ligands as CD28 but with much higher affinity and subsequently terminates T cell activation. The ligands for PD-1 and BTLA, PD-L1/PD-L2, and B7x, respectively, are expressed on immune cells as well as non-hematopoietic cells. Triggering of PD-1 or BTLA inhibits T cell proliferation and cytokine production. Lastly, B7-H3 is a new costimulatory ligand originally described to induce T cell proliferation and IFN- $\gamma$  production through an as of yet unidentified receptor. The recent generation of B7-H3-deficient mice, however, suggests that it is an inhibitory costimulator.

As positive costimulation can enhance T and B cell activation, inhibitory costimulation can just as strongly attenuate these responses. The final outcome of an immune response likely depends on the balance between these positive and negative signals.

Receptor: CD28 Family	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
CD28	T44	Costimulation	T and NK cells	B7.1	CD80	Activated APC
				B7.2	CD86	APC (upregulated) activated T cells

Receptor: CTLA-4	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
CTLA-4	CD152	Inhibition	Activated T cells	B7.1	CD80	Activated APC
				B7.2	CD86	APC (upregulated) activated T cells

Receptor: ICOS	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
ICOS	H4, CRP-1, AILIM	Costimulation	Activated T cells	B7RP-1	ICOSL, GL50, B7-H2, B7h	APC

Receptor: ?	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
?				B7-H3		

Inhibitory Molecules	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
PD-1		Inhibition	Activated T and B cells	PD-L1	B7-H1	Leukocytes
				PD-L2	B7-DC	Monocytes, macrophages, DC

Receptor: CTLA-4	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
CTLA-4	CD152	Inhibition	Activated T cells	B7.1	CD80	Activated APC
				B7.2	CD86	APC (upregulated) activated T cells

TNFR Family	Other names	Function	Expression	Ligand: TNF Family	Other names	Expression
CD27	T14	Costimulation	T cells, B subset, NK	CD70		Activated B cells
CD30	Ki-1	Costimulation, apoptosis	Activated T, NK and B cells	CD153	CD30L	Neutrophils, activated B and T cells

Receptor: CD40L	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
CD40L	CD154, gp39, TRAP	Activation	Activated T cells	CD40		APC T subset, endothelium, cardiac myocytes, fibroblasts

Receptor: 4-1BB	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
4-1BB	CD137	Costimulation	Activated T cells	4-1BBL		Activated B, DC, peritoneal cells

Receptor: OX-40	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
OX-40	CD134	Activation, differentiation, apoptosis	Activated T cells	OX-40L		Activated B cells, cardiac myocytes

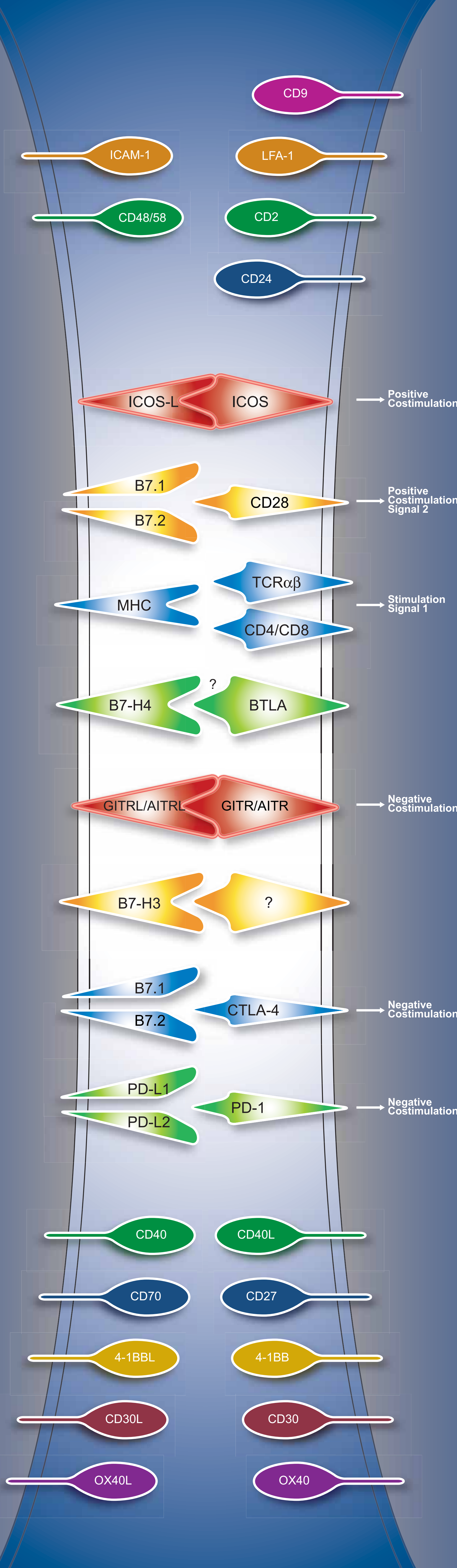
Receptor: Fas	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
Fas	CD95, Apo-1	Activation, apoptosis	Leukocytes	FasL	CD95L, CD178	Activated T cells

Receptor: AITR	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression
AITR	GITR	Costimulation	Treg, T (upregulated)	AITRL	GITRL, TL6	APC

Receptor: ?	Other names	Function	Expression	Ligand: B7 Family	Other names	Expression

References:  
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 Dieffenbach A, Jensen ER, Jamieson AM, Rautel DH. 2001. Rae1 and HV0 ligands of the NKG2D receptor stimulate tumour immunity. *Nature*. 413:165-169.

Compiled by Nooshan Alaverdi on September 2004  
 Art Design by Steven Lee



## T Cell

### eBioscience Products

Antibody Format Legend:  
 Purified: White (14)    PE-Cy5: Green (15)    APC: Light blue (17-)    PE-Cy7: Purple (24)  
 \*FG Purified: Yellow (16)    PE-Cy5: Pink (15)    APC-Cy7: Light purple (10-)    APC-Cy5.5: Lime Green (30)  
 Biotin: Orange (13-)

Mouse	Clone	Antibody Formats
CD2	RM2-5	14-0021, 16-0021, 13-0021, 12-0021
CD3 $\epsilon$	145-2C11	14-0031, 16-0031, 13-0031, 12-0031, 15-0031, 17-0031, 10-0031, 30-0031
CD3	17A2	14-0032
CD4	RM4-5	14-0042, 16-0042, 13-0042, 12-0042, 15-0042, 17-0042, 10-0042, 30-0042
CD4	OK1-5	30-0042, 35-0042
CD4	OK1-5	14-0041, 16-0041, 13-0041, 12-0041, 15-0041, 17-0041, 10-0041, 30-0041
CD5	53-7.3	14-0051, 16-0051, 13-0051, 12-0051
CD8a	53-6.7	14-0081, 16-0081, 13-0081, 12-0081, 15-0081, 17-0081, 10-0081, 30-0081
CD11a	M17/4	14-0111, 16-0111, 13-0111, 12-0111
CD11b	M17/0	14-0112, 16-0112, 13-0112, 12-0112, 15-0112, 17-0112, 10-0112, 30-0112
CD11c	N418	14-0114, 16-0114, 13-0114, 12-0114, 15-0114, 17-0114, 35-0114
CD19	G35	14-0199, 16-0199, 13-0199, 12-0199, 15-0199, 17-0199, 10-0199, 30-0199
CD19	MB19-1	14-0191, 16-0191, 13-0191, 12-0191, 15-0191, 17-0191
CD24	M1/69	14-0242, 16-0242, 13-0242, 12-0242, 15-0242, 17-0242
CD24	30-F1	14-0241, 16-0241, 13-0241, 12-0241
CD25	PC61.5	14-0251, 16-0251, 13-0251, 12-0251, 15-0251, 17-0251, 10-0251, 30-0251
CD27	LG-7F9	14-0271, 16-0271, 13-0271, 12-0271, 15-0271, 17-0271
CD28	37.51	14-0281, 16-0281, 13-0281, 12-0281, 15-0281, 17-0281
CD30	mCD30.1	14-0301, 16-0301, 13-0301, 12-0301
CD40	RM40-3	14-0409, 16-0409, 13-0409, 12-0409, 15-0409, 17-0409, 10-0409, 30-0409
CD40	IC10	14-0401, 16-0401, 13-0401, 12-0401, 15-0401, 17-0401
CD44	IM7	14-0441, 16-0441, 13-0441, 12-0441, 15-0441, 17-0441, 10-0441, 30-0441
CD54/ICAM-1	YN1/1.7.4	14-0541, 16-0541, 13-0541, 12-0541
CD62L/L-Selectin	MEL-14	14-0621, 16-0621, 13-0621, 12-0621, 15-0621, 17-0621, 10-0621
CD69/VEA	H1-2F3	14-0691, 16-0691, 13-0691, 12-0691, 15-0691, 17-0691
CD70/CD27L	FR70	14-0701, 16-0701, 13-0701, 12-0701
CD80/B7.1	16-10A1	14-0801, 16-0801, 13-0801, 12-0801, 15-0801, 17-0801
CD81/TAPA-1	Ea-2	14-0811, 16-0811, 13-0811
CD83	M16/17	14-0831, 16-0831, 13-0831, 12-0831
CD86/B7.2	PO-1	14-0861, 16-0861, 13-0861, 12-0861, 15-0861, 17-0861
CD86/B7.2	GL1	14-0862, 16-0862, 13-0862, 12-0862, 15-0862, 17-0862
CD90/Thy1	G7	14-0901, 16-0901
CD90.1	HIS51	14-0900, 16-0900, 13-0900, 12-0900, 15-0900, 17-0900
CD90.2	53-2.1	14-0902, 16-0902, 13-0902, 12-0902, 15-0902, 17-0902
CD90.2	30-H12	14-0903, 16-0903, 13-0903, 12-0903, 15-0903
CD95/Fas	15A7	14-0951, 16-0951, 13-0951, 12-0951
CD134/OX-40	S14	14-1341, 16-1341, 13-1341, 12-1341
CD134/OX-40	TM-31	14-1321, 16-1321, 13-1321, 12-1321
CD134/OX-40	OX-86	14-1341, 16-1341, 13-1341, 12-1341
CD137/4-1BB	17B5	14-1371, 16-1371, 13-1371, 12-1371
CD150/SLAM	Please Inquire!	14-1501, 16-1501, 13-1501, 12-1501
CD152/CTLA-4	UC10-4B9	14-1522, 16-1522, 13-1522, 12-1522
CD152/CTLA-4	8H10	14-1521, 16-1521
CD153/CD30L	RM153	14-1531, 16-1531, 13-1531, 12-1531
CD154/CD40L	RM1	14-1541, 16-1541, 13-1541, 12-1541
CD178/FasL	MFL3	14-5911, 16-5911, 13-5911, 12-5911
CD178/FasL	MFL4	14-5912, 16-5912
CD209/DC-SIGN	Please Inquire!	
4-1BBL	TKS-1	14-5901, 16-5901, 13-5901, 12-5901
B7-H3	Please Inquire!	14-5973, 16-5973, 13-5973, 12-5973
B7-H4	188	14-5972, 16-5972, 13-5972, 12-5972
B7-H4	clone 9	14-5970, 16-5970, 13-5970, 12-5970
BTLA	Please Inquire!	14-5851, 16-5851, 13-5851, 12-5851
GITR	DTA-1	14-5871, 16-5871, 13-5871, 12-5871, 15-5871, 17-5871
ICOS	C388.4A	14-9949, 16-9949, 13-9949, 12-9949, 15-9949, 17-9949
ICOS	7E-1709	14-9942, 16-9942, 13-9942, 12-9942, 15-9942
ICOS	15F9	14-9940, 16-9940, 13-9940, 12-9940
ICOSL/B7RP-1	HK5.3 (blocking)	14-5985, 16-5985, 13-5985, 12-5985
MHC class I	28-14-8	14-5999, 16-5999, 13-5999, 12-5999
MHC class I	34-1-2S	14-5998, 16-5998, 13-5998, 12-5998
MHC class II	MS114.15.2	14-5321, 16-5321, 13-5321, 12-5321, 15-5321, 17-5321
MHC class II	14-4-4S	14-5309, 16-5309, 13-5309, 12-5309
NKG2D	A10 (activating)	14-5872, 16-5872, 13-5872, 12-5872
NKG2D	CT (blocking)	14-5873, 16-5873, 13-5873, 12-5873, 17-5873
NKG2D	CX5 (blocking)	14-5882, 16-5882, 13-5882, 12-5882, 17-5882
NKG2D	Mi6	14-5880, 16-5880
OX-40L	RM134L (blocking)	14-5905, 16-5905, 13-5905, 12-5905
PD-1	RMP1-14	14-9982, 16-9982
PD-1	RMP1-30	14-9981, 16-9981, 13-9981, 12-9981
PD-1	J43	14-9989, 16-9989, 13-9989, 12-9989
PD-L1/B7-H1	1-111A	14-9971, 16-9971
PD-L1/B7-H1	MIH5	14-9982, 16-9982, 13-9982, 12-9982
PD-L2/B7-DC	122	14-9972, 16-9972, 13-9972, 12-9972
PD-L2/B7-DC	TY25 (blocking)	14-9986, 16-9986, 13-9986, 12-9986
RAE-1 $\gamma$	CX1	14-5881, 16-5881, 13-5881, 12-5881
TCR $\alpha\beta$	H57-59D	14-5961, 16-5961, 13-5961, 12-5961, 15-5961, 17-5961, 10-5961, 30-5961
TCR $\gamma\delta$	UC7-13D5	14-5811, 16-5811, 13-5811, 12-5811
ZAP-70	1E7.2	14-6695, 16-6695, 13-6695, 12-6695, 35-6695

Human	Clone	Antibody Formats
CD2	RPA-2.10	14-0029, 16-0029, 13-0029, 12-0029
CD3	OKT3	14-0037, 16-0037, 13-0037, 12-0037
CD3	UCHT1	14-0038, 16-0038, 13-0038, 12-0038, 15-0038, 17-0038, 10-0038, 30-0038
CD3	HIT3A	14-0039, 16-0039, 13-0039, 12-0039
CD4	RPA-T4	14-0049, 16-0049, 13-0049, 12-0049, 15-0049, 17-0049, 10-0049, 30-0049
CD4	HI100	14-0059, 16-0059, 13-0059, 12-0059, 15-0059, 17-0059
CD8a	RPA-T8	14-0089, 16-0089, 13-0089, 12-0089, 15-0089, 17-0089, 10-0089, 30-0089
CD11a	HI111	14-0119, 16-0119, 13-0119, 12-0119
CD11b	CBRM1/5	14-0113, 16-0113, 13-0113, 12-0113
CD11b	ICRF44	14-0118, 16-0118, 13-0118, 12-0118
CD11c	3.9	14-0116, 16-0116, 13-0116, 12-0116
CD19	HIB19	14-0199, 16-0199, 13-0199, 12-0199, 15-0199, 17-0199, 10-0199, 30-0199
CD20	2H7	14-0209, 16-0209, 13-0209, 12-0209, 15-0209, 17-0209
CD25	2A6	14-0259, 16-0259, 13-0259, 12-0259, 15-0259
CD27	O323	14-0279, 16-0279, 13-0279, 12-0279, 15-0279, 17-0279
CD27	LG-7F9	14-0271, 16-0271, 13-0271, 12-0271, 15-0271, 17-0271
CD28	CD28.2	14-0289, 16-0289, 13-0289, 12-0289, 15-0289, 17-0289
CD28	16-0288	16-0288
CD40	5C3	14-0409, 16-0409, 13-0409, 12-0409
CD44	IM7	14-0441, 16-0441, 13-0441, 12-0441, 15-0441, 17-0441, 10-0441, 30-0441
CD44	RA88	14-0449, 16-0449, 13-0449, 12-0449, 15-0449, 17-0449