

## Overview

The recent revival of the "suppressor T cell" concept described originally in the 1970's has resulted in a dramatic and important quest to characterize the true identity of the cells participating in normal immune homeostasis and to explain the molecular mechanisms involved. This renewed interest was initiated by the identification of a discrete CD4<sup>+</sup>CD25<sup>+</sup> T cell subset regulating self-tolerance, hence the "regulatory T cell" or "Treg" nomenclature now in use. The accumulating data characterizing with greater detail than ever before the phenotype and function of these regulatory T cells has generated interest in studying Treg cells, not only from the point of view of basic research, but also from a clinical point of view for the implications in cellular therapy.

Initial research into the phenotype and function of Tregs generally utilized bulk Treg cell preparations propagated by *in vitro* culture systems. These studies mainly suggest a cell-cell contact-dependent mechanism involving IL-2 for Treg-mediated suppression in a wide spectrum of responses to auto-antigens, transplants, microbial pathogens, and tumors. Additional studies support a mechanism of bystander suppression and dependence on IL-10 and/or transforming growth factor  $\beta$  (TGF- $\beta$ ) secreted by Treg populations, as well as the possibility of direct killing through a perforin-dependent means.

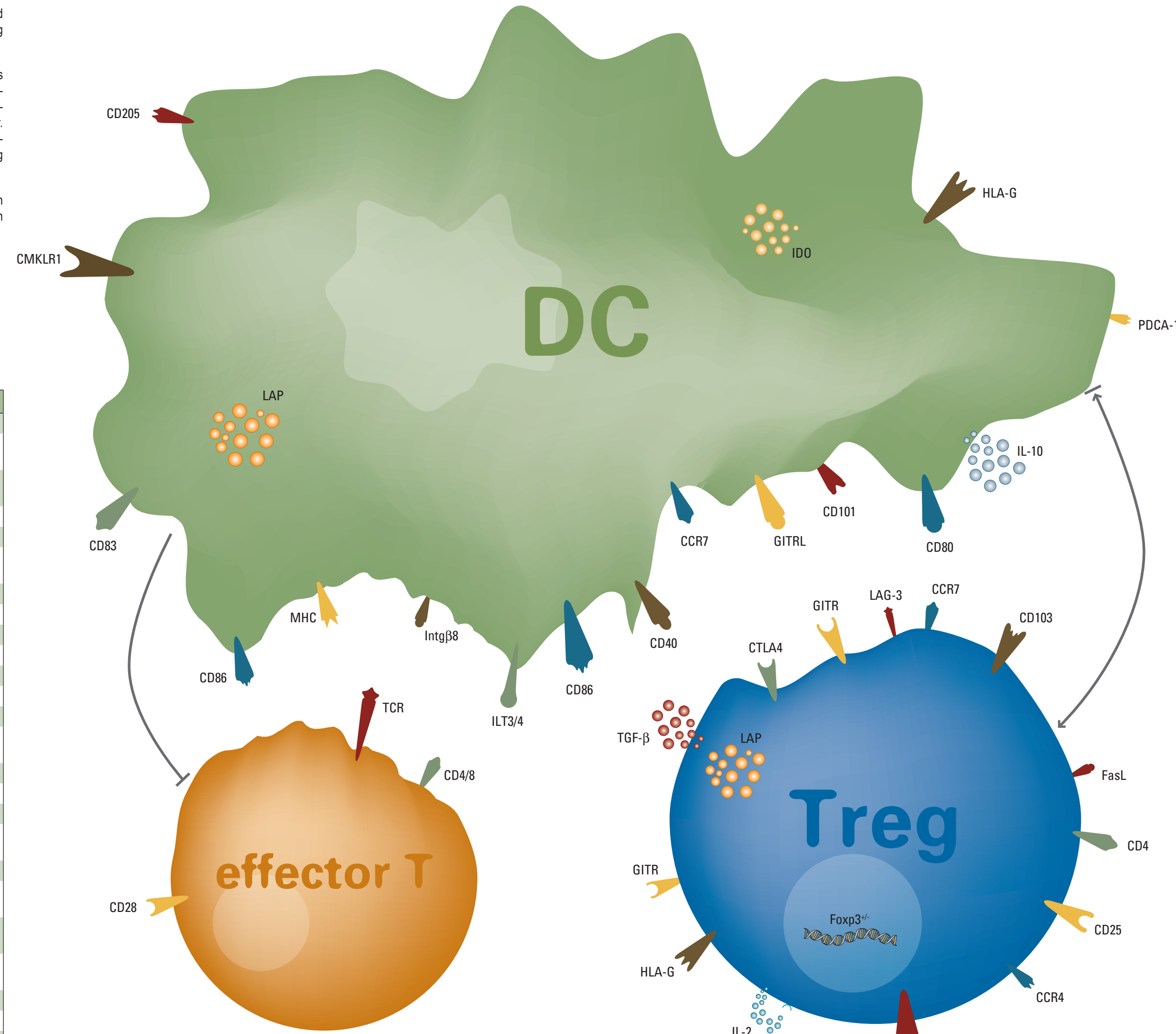
To discriminate bystander suppression, to better elucidate the role of Tregs in maintaining self-tolerance, and to harness their immunosuppressive properties in prevention of allograft rejection, research is now focused on antigen-specific/alloantigen-specific Treg cells. Furthermore, recent investigations have sought to examine whether the multiple modes of action proposed from *in vitro* studies correlate with the behavior of these cells *in vivo*. Studies from both *in vitro* and *in vivo* systems have clearly demonstrated a complex dialogue between antigen presenting cells (APC) and Tregs. Two-photon laser-scanning microscopy (TPLSM) studies provide evidence that Treg limit the access of effector T cells to dendritic cells (DC). A subset of APC, DCs are the most efficient cell type for antigen uptake/presentation and priming of mature T cells. These recent *in vivo* studies show that antigen-specific Treg cells directly interact with DCs, forming long-lasting cell conjugates and preventing the clustering of DCs with effector cells. Moreover, by TPLSM analysis, stable cell-cell interactions between Treg and effector T cells are not observed. DCs are central to Treg function *in vivo* and one interpretation of these recent TPLSM studies is that Treg cells target and directly inactivate DC function, and perhaps also dampen the stability of effector T-DC interactions.

For the purposes of highlighting this interaction, an illustration of a "Treg", a "DC", and an "Effector T cell" interacting with each other depicts the complex mechanisms and the multitude of cell surface contact-dependent and cytokine-dependent interactions among these cells. Molecules reported to have important roles in the interaction between Treg and DC, between DC and Effector T, as well as between Treg and Effector T have been illustrated. It should be noted that the exact type of Treg or DC as well as the stoichiometry of this interaction is still unclear. Different types of DC (including plasmacytoid DC (pDC), myeloid DC (mDC), and *in vitro*-bone marrow-derived DC in their various maturation/activation states) have all been reported to interact with and shape Treg development and function. Similarly, different subtypes of Treg cells (including CD4<sup>+</sup>CD25<sup>+</sup>, IL-10-secreting Treg (Tr1), and others) may be important in controlling a specific type of immune response.

Many facets of the interaction of Treg with DC and other APC and the molecular mechanisms involved in immune suppression/regulation remain unclear and undoubtedly will remain the focus of intensive, ongoing research well into the future. To update this illustration based on your findings, we welcome your suggestions, please contact [tech@ebioscience.com](mailto:tech@ebioscience.com).

References: J. Exp. Med. 2006. 203:505. Nature Immunol. 2006. 7:83 and 7:11. Immunol Reviews. 2006. 212:314. J. Exp. Med. 2004. 199:1467.

# The Expanding Complexity of the Dendritic Cell - Regulatory T Cell Dialogue



## Molecules in DC-Treg Dialogue

Molecule	Biological Relevance	References
CD46	Reported for <i>in vitro</i> expansion of Treg	J Clin Invest. 2006. 116:3252.
CD62L	Lymph node (LN) homing selectin, CD103 <sup>+</sup> CD62L <sup>+</sup> Treg home to LN and exhibit potent suppressor function	Am J Transplant. 2004. 4:65.
CD80 & CD86	Treg interaction downregulates these on DCs. CD80 and CD86 have opposing roles	Immunol Rev. 2006. 212:314.
CD85g/ILT7	Expressed exclusively by pDC	J Exp Med. 2006. 203:1399.
CD101/B27	Expressed by DC subsets, reported to activate/expand nTreg <i>in vitro</i>	Eur J Immunol. 2000. 30:3132.
CD103/Integrin $\alpha$ E $\beta$ 7	CD103 <sup>+</sup> CD62L <sup>+</sup> Treg home to inflammatory sites and the gut, role in suppressing response to L. major, expressed on intestinal DC and role in colitis	J Immunol. 2005. 174:5444.
CD127/IL-7R $\alpha$	Downregulated on Treg resulting in low homeostatic proliferation	J Exp Med. 2006. 203:1693.
CD152/CTLA-4	Expressed on the surface of Treg, interacts with CD80, CD86 on DC	J Exp Med. 2000. 192:295.
CD178/FasL	Expressed by CCR4 <sup>+</sup> human blood Treg	J Immunol. 2007. 178:4891.
CD194/CCR4	Expressed by 75% of human peripheral blood Treg	J Immunol. 2007. 178:4891.
CD197/CCR7	Expressed by some Treg, homing to LN	J Exp Med. 2007 Mar 19.
CD205/DEC205	Antigen uptake receptor on DC	Nat Immunol. 2005. 6:1219.
CD207/Langerin	Expressed by DC subset, Langerhans Cells/LC. Role in antigen uptake	J Immunol. 2002. 168:782.
CD209/DC-SIGN	DC marker. Primes DCs to induce Treg	J Allergy Clin Immunol. 2005. 115:1260.
CMKLR1	Expressed by pDC. Receptor for chemerin	J Immunol. 2005. 174:244.
DCIR	C-type lectin inhibitory receptor, expressed by APC and granulocytes	Immunobiology. 2004. 209:179.
DC-LAMP	DC maturation marker, lysosomal distribution	Immunity. 1998. 9:325.
GILZ	GILZ-expressing DC + IL-10 promote antigen-specific Treg development, differentiation of DC into regulatory DC.	Blood. 2006. 107:2037.
GITR	Expressed by mouse nTreg, function unclear	Nat Immunol. 2002. 3:135.
GRAIL	E3 ubiquitin ligase, upregulated in nTreg. Role in regulatory function of these cells.	J Biol Chem. 2007 Jan 26.
IDO	Indoleamine 2,3-dioxygenase, tryptophan catalysis, expressed by tolerogenic DC	Med Mycol. 2006. 44:237.
IL-2	Required for thymic/peripheral Treg development and <i>in vitro</i> Treg expansion.	J Exp Med. 2005. 201:769.
IL-10	IL-10-induced DC expand Treg <i>in vitro</i> , produced by DC and other cells.	Eur J Immunol. 2007. 37:177.
IL-27	Produced by DC and other APC, initiator of Th1 response	Infect Immun. 2006. 74:1480.
IL-28 & IL-29	IFN- $\gamma$ induces tolerogenic DCs and Foxp3 <sup>+</sup> Treg	Blood. 2006. 107:4417.
ILT3, ILT4	Expressed by IL-10-induced DC, induces Tr1 development.	Transpl Immunol. 2003. 11:245.
Integrin $\alpha$ 4 $\beta$ 7	Mucosal homing receptor, upregulated on Treg cultured with DC and on CD45RB <sup>hi</sup> CD4 <sup>+</sup> T cells.	Immunol Lett. 2004. 94:11.
Integrin $\alpha$ V $\beta$ 8	Expressed by DC. Activates TGF- $\beta$ from latent TGF- $\beta$ and induce Foxp3 expression	J Cell. Bio. 2002. 157:493.
Neuropilin-1	Semaphorin III receptor, co-expressed with Foxp3 in nTreg, DC-T homophilic interactions	Eur J Immunol. 2004. 34:623.
Notch-1	Notch receptors. Jagged-1/Serrate1 expressed by APC. Reported to drive Treg differentiation	Immunol Lett. 2004. 94:11.
PDCA1/BST2	Expressed by naive pDC/IPC, upregulated on many cells	J Immunol. 2006. 177:3260.
Siglec H	Expressed by pDC/IPC; interacts with DAP12	Blood. 2006. 107:2474.
Stat1, Stat5	Required for Treg development/function; may maintain CD25 expression.	J Immunol. 2003. 171:3435.
TGF- $\beta$ 1	Produced by DC and other cells (Th3 and Tr1). Promotes Treg development and expansion. Induces Foxp3 expression	PNAS. 2004. 101:4572.
Memb-TGF- $\beta$ 1	Expressed by Treg on the surface	PNAS. 2003. 100:10878.
TSLP & TSLPR	Thymic stromal lymphopoietin. Induces Foxp3	Nat Immunol. 2006. 7:709.
Vitamin D & Receptor	Expressed by both human myeloid DC and pDC. Vitamin D promotes Treg development <i>in vitro</i>	J Immunol. 2007. 178:145.

Due to the large number of articles pertaining to DC and Treg biology, only one review or recent article has been cited for each antigen/comment. Please contact eBioscience technical support for comprehensive literature citations.

## Product Listing

For ordering information and available formats, please visit [www.ebioscience.com](http://www.ebioscience.com). We offer antibodies in the following formats: Purified, FG Purified, Biotin, FITC, PE, PE-Cy5, APC, Cy5, APC-Cy7, PE-Cy7, APC-Cy5.5, PE-Cy5.5, Alexa Fluor<sup>®</sup>, and Pacific Blue<sup>®</sup>.

### Product Abbreviations:

- Rec - Recombinant Protein (available with carrier or carrier-free)
- Set - ELISA Set (with or without uncoated plates)
- Kit - ELISA Kit (with precoated plates)
- Spot - ELISPOT Set

Antigen	Human	Mouse
33D1 (DC Marker)	-	33D1
3G11	-	eBio3G11
BAMBI	4E8	-
CD4	OKT4, RPA-T4	GK1.5, RM4-5, RM4-4
CD8a	RPA-T8, HIT8a	53-6.7
CD11c	3.9	N418
CD25	BC96	PC61.5, eBio7D4, eBio3C7
CD28	CD28.6 (blocking), CD28.2 (costimulatory)	37.51
CD40	5C3	1C10, HM40-3
CD45RA	HI100, JS-83	-
CD45RB	MEM-55	C363.16A
CD45RO	UCHL1	-
CD46	8E2	-
CD62L	DREG-56	MEL-14
CD80	2D10.4	16-10A1
CD83	HB15e	Michel-17
CD85g/ILT7	eBio17G10.2	-
CD86	IT2.2	PO3.1, GL1
CD103	B-Ly7	2E7
CD127/IL-7R $\alpha$	eBioRDR5	A7R34
CD134/OX40	ACT35	OX-86
CD152/CTLA4	14D3, eBio20A	9H10, UC10-4B9
CD197/CCR7	CCR7.6B3	4B12
CD198/CCR8	polyclonal	-
CD205/DEC205	MG38	-
CD207/Langerin	-	eBioRMUL2, eBioL31
CD209/DC-SIGN/CIRE	polyclonal, eB-h209	LWC06, 5H10
CD223/LAG-3	-	eBioC9B7W Set
CD252/OX40L	eBioik-5, eBio11C3.1	RM134L
CD273/B7-DC	MIH18	TY25, 122
CD289/TLR9	eB72-1665	polyclonal, M9.D6
CMKLR1	BZ332	-
FLT3L	Rec	-
Foxp3	PCH101, 236A/E7, eBio7979, 150D/E4	FJK-16s, eBio7979, NRRF-30, 150D/E4
GILZ	polyclonal, mAb	polyclonal, mAb
GITR/AITR	eBioAITR	DTA-1
GITRL/AITRL	eBioAITR-L	eBioYGL386
IL-2	polyclonal, MQ1-17H12 Rec, Set, Kit	JES5-1A12, JES6-5H4 Rec, Set, Kit, Spot
IL-10	JES3-9D7, JES3-12G8 Rec, Set, Kit, Spot	JES5-16E3, JES5-2A5 Rec, Set, Kit, Spot
IL-12 p70	B-T21 Rec, Set, Kit, Spot	C18.2 Rec, Set, Kit
IL-12/23 total p40	C8.3, C8.6 Rec	C15.6, C17.8 Set, Kit
IL-15	Rec	polyclonal, AIO.3 Rec, Set
IL-15R $\alpha$	eBioJM7A4	-
IL-28	-	Rec
IL-29	Rec, Set, Spot	-
Integrin $\alpha$ 4 $\beta$ 7/LPAM-1	-	DATK32
Ly6C	-	mAb
Mac2/Galectin 3	eBioB2C10	eBioM3/38
Neuropilin	-	polyclonal
PDCA-1/BST2	-	eBio129c, eBio927
PPAR $\gamma$	polyclonal	polyclonal
RelB	mAb	mAb
Siglec H	-	eBio440c
SIGN-R1	-	eBio22D1
TGF- $\beta$ 1	Rec, Set, Kit	Rec, Set, Kit
TSLP	eBio15B11.3, eBio13H8.3	eBio28F12, eBio65B12
TSLP-R	eBio1D8, eBio1A6	-
WASP	polyclonal	polyclonal

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